INFECTIOUS AND INFLAMMATORY DISEASES OF THE CNS

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INTRODUCTION

Animals with meningoencephalomyelitis (MEM) typically are presented for acutely progressive, focal to multi-focal neurological signs. Patients should be stabilized initially if systemic derangements (cardiovascular or respiratory) or evidence of increased ICP are/is present. When the patient is stable, the clinician should attempt to differentiate between infectious and idiopathic MEM based on the signalment, physical examination findings, the presence/absence of systemic signs, and infectious disease testing. Differentiation between infectious and idiopathic MEM is critical, and may require CSF analysis and advanced neuroimaging. Once an infectious or idiopathic differential diagnosis list is generated, the most appropriate diagnostic plan can be implemented.

MENINGOENCEPHALOMYELITIS

Overview

MEM is defined as inflammation of the meninges (dura, arachnoid and pia mater) and the neuroparenchyma (e.g. forebrain, brainstem, cerebellum and/or spinal cord). Clinical signs of encephalitis reflect the location of the lesion(s) (forebrain, brainstem or cerebellum). Clinical signs of myelitis reflect whether the spinal cord lesion(s) are within the UMN or LMN system, or both. Pain and/or hyperaesthesia is/are most common with meningitis (brain or spinal cord).

Due to the typical acute and progressive nature of MEM, animals are commonly presented for emergency evaluation. Based on the neuroanatomical localization, it is imperative to formulate an accurate differential diagnosis in order to institute the correct diagnostic recommendations and therapies.

Aetiology/pathophysiology

MEM may be caused by an infectious agent or associated with an idiopathic inflammatory condition of the CNS. Canine and feline MEM have been reported throughout the world. However, infectious MEMs are more prevalent in certain geographical locations (*Table* 77).

Table 77	**Global prevalence of infectious MEM***
REGION	**INFECTIOUS AGENTS**
North America	*A. platys, Aspergillus* spp., *Babesia* spp., *B. dermatitidis,* CDV, *C. immitis, C. neoformans, E. canis,* FIPV, *H. capsulatum, N. caninum,* rabies virus, *R. rickettsii, T. gondii*
Central America	*B. dermatitidis,* CDV, *C. immitis,* FIPV, *N. caninum,* rabies virus, *T. gondii*
South America	CDV, *C. immitis, C. neoformans,* FIPV, *H. capsulatum, N. caninum,* rabies virus, *R. rickettsii, T. gondii*
Europe	*Aspergillus* spp., *B. dermatitidis,* CDV, *C. neoformans, E. canis,* FIPV, *N. caninum,* rabies virus, *R. rickettsii, T. gondii*
Northern Asia	CDV, *C. neoformans, E. canis,* FIPV, rabies virus, *T. gondii*
Southeast Asia	*B. dermatitidis,* CDV, *C. neoformans, E. canis,* FIPV, rabies virus, *T. gondii*
Africa	*B. dermatitidis,* CDV, *C. neoformans, E. canis,* FIPV, rabies virus, *T. gondii*
Australia	*A. platys, Aspergillus* spp., CDV, *C. neoformans, E. canis,* FIPV, rabies virus, *T. gondii*

*Risk of exposure to the most common diseases in these areas. Great Britain, Scandinavia, New Zealand, Japan and much of Australia are considered rabies 'free'.

AGENT	DOGS	CATS
Bacterial	Aerobic Anaerobic	Aerobic Anaerobic
Rickettsial	*Rickettsia rickettsii* *Ehrlichia* spp. *Anaplasma* spp.	
Viral	Canine distemper virus (CDV) Rabies virus West Nile virus (North America) Tick-borne encephalitis virus (Europe and Asia) Borna disease virus (Europe and Japan) Eastern equine encephalitis virus (North America; rare)	Feline infectious peritonitis virus (FIPV) Feline leukaemia virus (FeLV) Borna disease virus (Europe and Japan)
Protozoal	*Neospora caninum* *Toxoplasma gondii* *Sarcocystis canis* (rare) *Encephalitozoon cuniculi* (rare) *Trypanosoma cruzi* (rare) *Acanthomoeba* spp. (rare) *Babesia* spp. (rare) *Leishmania* spp. (Mediterranean basin and Portugal)	*Toxoplasma gondii* *Babesia* spp. *Leishmania* spp. (Mediterranean basin and Portugal)
Fungal	*Cryptococcus* spp. *Coccidioides immitis* *Blastomyces dermatitidis* *Histoplasma capsulatum* (rare) *Aspergillus* spp. (rare)	*Cryptococcus* spp. *Coccidioides immitis* *Blastomyces dermatitidis* *Histoplasma capsulatum* (rare) *Aspergillus* spp. (rare)
Parasitic	Cuterebra larva migration (rare) *Dirofilaria immitis* – abberant migration (rare)	Cuterebra larva migration (rare) *Dirofilaria immitis* – abberant migration (rare)

Table 78 **Infectious agents known to cause acute meningoencephalomyelitis**

Infectious meningoencephalomyelitis

Infectious agents are confirmed uncommonly in cases of MEM, but are important differentials nonetheless. Pathogens that may cause canine or feline MEM include bacteria, viruses, protozoa, fungi, and parasites. MEM most commonly occurs in young or immuno-compromised animals; however, any dog or cat may develop a CNS infection. Some infectious agents are capable of affecting multiple organ systems in addition to the CNS, which may prove helpful in distinguishing CNS infections from an idiopathic meningoencephalitis (ME). The severity of infection is dependent on several factors including: the status of the animal's immune system at the time of inoculation; strength of the animal's immune response during active infection; nutritional status of the animal; strain and virulence factors of the infectious agent; and environmental factors. Clearance of the infectious agents is dependent on these factors as well; however, some pathogens may enter a dormant stage within the host without producing clinical disease. Recrudescence of such organisms may occur with or without clinically apparent disease.

Infectious agents known to cause acute MEM in the dog and cat are listed in *Table 78*.

Bacterial and rickettsial meningoencephalomyelitis

Bacterial meningitis and CNS abscesses are among the most important differentials for MEM that may lead to an emergency presentation. Bacterial meningitis may result from several different mechanisms including: haematogenous spread from other foci within the body; direct inoculation from traumatic wounds or needles following CSF acquisition; or direct extension from other structures of the head (eyes, ears, cribriform plate). Bacteria that have been reported in association with meningitis include *Staphylococcus* spp., *Pasteurella* spp., *Escherichia coli*, *Actinomyces* spp., *Nocardia* spp., *Klebsiella* spp., *Peptostreptococcus* spp., *Eubacterium* spp. and *Bacteroides* spp. Pathological findings include infiltration of mononuclear and polymorphonuclear (PMN) cells into the leptomeninges. If the underlying neuroparenchyma is affected, necrosis of the grey and white matter may occur due to direct neuronal injury or thrombosis.

CNS abscesses and empyema, similar to bacterial meningitis, may result from haematogenous spread from other foci within the body, direct inoculation or direct extension from other structures of the head (nasal cavity and sinuses, eye, ear). Immature and immunocompromised animals are at a greater risk for the development of CNS abscesses. Similar organisms to those responsible for bacterial meningitis have been reported including *Staphylococcus* spp., *Streptococcus* spp., *Nocardia* spp., *Pasteurella* spp., *Actinomyces* spp., *Fusobacterium* spp., *Bacteroides* spp. and *Peptostreptococcus* spp. Occasionally, fungal organisms may produce CNS abscesses. The progression of abscess formation includes inflammation of the associated anatomical structure (i.e. encephalitis, myelitis) followed by capsular formation. Oedema and significant mass effect are often features of this disease in the brain (**269**). Additional pathological findings include rings of organisms with infiltration of mononuclear and PMN cells, diffuse leptomeningitis, reactive astrocytes, gliosis and cerebral oedema outside the capsule.

Rickettsial organisms, including *Rickettsia rickettsii* and *Ehrlichia canis*, are transmitted to dogs via tick vectors. Once rickettsiae infect a dog or cat, they enter endothelial cells, leading to a vasculitis of multiple organ systems including the CNS. Lymphoplasmacytic meningitis predominates; however, MEM occurs occasionally when the underlying neuroparenchyma (forebrain, brainstem and cerebellum) is affected.

▲ **269** **Transverse T1-weighted post-contrast (a) and T2-weighted (b) images of the brain of a cat with subdural empyema (arrows) causing severe mass effect with marked displacement of the falx cerebri. (Photo courtesy Laurent Garosi)**

Viral meningoencephalomyelitis

Recently, there have been sporadic reports of flavivirus (tick-borne encephalitis virus, west Nile virus), bornavirus and Eastern equine encephalitis infection in dogs, suggesting that canine viral ME is more prevalent than currently accepted. However, the aetiologies for the majority of cases of canine ME remain elusive, potentially because of current limitations for pathogen detection in routine diagnostic testing. The most common viral causes of acute MEM appear to be rabies and canine distemper virus (CDV).

Rabies infections have been reported more frequently in cats than in dogs in the US, with infection being uniformly fatal in both species. Rabies virus is considered endemic in most of the world except Great Britain, Scandinavia, New Zealand, Japan and much of Australia. After the virus is introduced through a bite of an infected animal, it then replicates and travels within peripheral nerves to the brain, resulting in a non-suppurative polioencephalomyelitis and craniospinal ganglionitis. The incubation period is 2 weeks to 6 months. Areas of the CNS affected are widespread and commonly include the brainstem and cerebral hemispheres. Occasionally, dogs and cats can develop post-vaccinal rabies if the vaccine is given during times of stress (e.g. boarding, surgery, systemic illness).

CDV, in contrast to rabies, is not uniformly fatal. Three forms of CDV occur in dogs, with encephalomyelitis in immature dogs (3–6 months of age most frequently) presenting most commonly as an acute neurological emergency. The other forms occur in adult to geriatric dogs, which are rarely presented for acute neurological signs. Dogs are inoculated with the virus via exposure to infected respiratory droplets. An infected dog with CDV can transmit the virus up to 60–90 days post infection. The virus spreads haematogenously to other organ systems including skin, endocrine and exocrine glands, epithelium of the gastrointestinal, respiratory and genitourinary tracts, and the CNS. Direct viral replication results in neuronal injury and necrosis, with multifocal lesions in grey and white matter. In the subacute stages, white matter tends to be more affected than grey matter. CNS lesions generally consist of varying degrees of lymphoplasmacytic inflammation, demyelination and necrosis. Post-vaccinal canine distemper encephalitis typically occurs in dogs <6 months of age and is associated with administration of a live virus. The pathogenesis is speculative, but may involve immunosuppression of the dog, latent CDV infection, inadequate attenuation of the vaccine or other vaccine component interactions.

FIP virus is the causative agent of CNS FIP, a syndrome that is uniformly fatal in cats. FIP virus is a mutated strain of the non-pathogenic feline enteric coronavirus. FIP occurs in two clinical forms: the effusive (wet) form and the non-effusive (dry) form. The more common effusive form causes systemic disease secondary to an exuberant humoral immune response, characterized by a fibrinous peritonitis and pleuritis. The non-effusive form results from a combined humoral immune and partial cell-mediated immune response. This 'eye and brain' form affects the meninges, CNS neuroparenchyma and uvea. Pathological findings within the CNS include perivascular pyogranulomatous infiltration of the leptomeninges, neuroparenchyma of the brain and spinal cord, choroid plexus and ependyma. Other common findings include subependymal necrosis, ventricular dilatation, hydrocephalus, panophthalmitis and vascular degeneration.

Protozoal meningoencephalomyelitis

Protozoal organisms are important causes of MEM in dogs and cats. Dogs and cats are the definitive hosts for *Neospora caninum* and *Toxoplasma gondii*, respectively. Transmission of *T. gondii* occurs by carnivorous ingestion (most common), orofaecal contamination or transplacentally. Multiple organ involvement, including ocular, pulmonary, liver and CNS, is often present concurrently. A mixed cell infiltrate predominated by lymphocytes is typically present. Clinical toxoplasmosis most commonly affects dogs <1 year of age and immunocompromised geriatric dogs. Toxoplasmosis may be associated with CDV or other infections, such as ehrlichiosis, or with glucocorticoid therapy. Neurological signs associated with *T. gondii* infection include MEM and/or myositis–polyradiculoneuritis.

The life cycle of *N. caninum* is not completely understood, but infection during the neonatal period is suspected. In addition to encephalomyelitis, multiple organ system involvement may also occur with *N. caninum* infection. In juvenile dogs <6 months of age, myositis, ascending polyradiculoneuritis and encephalomyelitis predominate. Rigid limb contracture and arthrogryposis may occur as a result of the myositis. Severe MEM tends to be rare with *N. caninum* infection in young dogs. In dogs >1 year of age, MEM (commonly cerebellitis) is the more typical presentation (**270**).
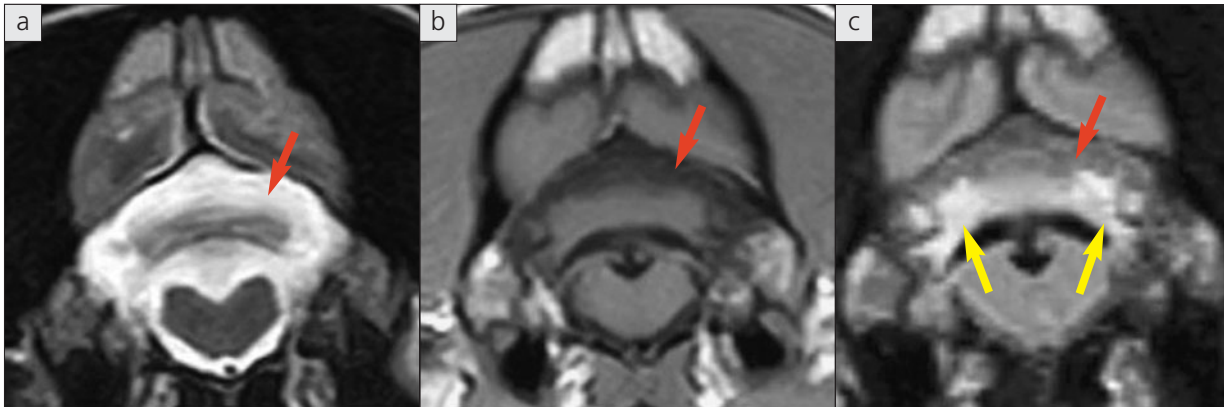
▲ **270** **Transverse T2-weighted (a), T1-weighted (b) and T2-weighted FLAIR (c) images of the caudal fossa of a 9-year-old West Highland White Terrier with** *Neospora* **infection. The diffusely atrophied cerebellum is surrounded by a thick T2-weighted hyperintense and T1-weighted hypointense signal that does not suppress on FLAIR sequences (red arrow). Additionally, there are bilaterally symmetrical FLAIR hyperintensities within the cerebellar white matter (yellow arrows). (Photo courtesy Laurent Garosi)**

Fungal and parasitic meningoencephalomyelitis

Mycotic agents sporadically cause MEM in dogs and cats. *Cryptococcus neoformans* is the most common CNS fungal infection in cats and dogs. *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Aspergillus* spp. have also been reported to cause CNS infection in dogs. The most common route of inoculation for fungal organisms is inhalation. Morphological conversion to the yeast form occurs in the animal and haematogenous or lymphatic spread to other organ systems, including the respiratory, skeletal, integument, ocular and musculoskeletal systems, may occur. Fungal organisms may cause an acute, focal or multifocal-diffuse MEM with a mixed cell parenchymal infiltrate (granulomatous or pyogranulomatous). Aberrant migration of parasitic larvae to the CNS, including *Cuterebra* spp. (common in cats) and *Dirofilaria immitis*, may also produce MEM in dogs and cats.

Idiopathic meningoencephalomyelitis

Idiopathic MEM occurs commonly in the dog, but seems to be extremely rare in the cat. GME, NME, NLE, SRMA and idiopathic tremor syndrome comprise the most common inflammatory conditions of the canine CNS. While each disease has unique histopathological features, these canine MEMs collectively seem to be aberrant immune responses directed against the CNS.

The aetiopathogenesis of GME, NME and NLE is probably multifactorial: familial predisposition, infectious agents and immunopathologic mechanisms all may play a role in disease pathogenesis. GME is responsible for up to 25% of canine CNS disease. Three morphological forms of GME have been described: disseminated, focal and ocular. Typical histopathological lesions include concentric proliferation of inflammatory cells around blood vessels, predominantly of the white matter of the CNS (**271**, next page). Clinical signs reflect the location of the lesions, and GME typically is fatal if not treated aggressively with immunosuppression.
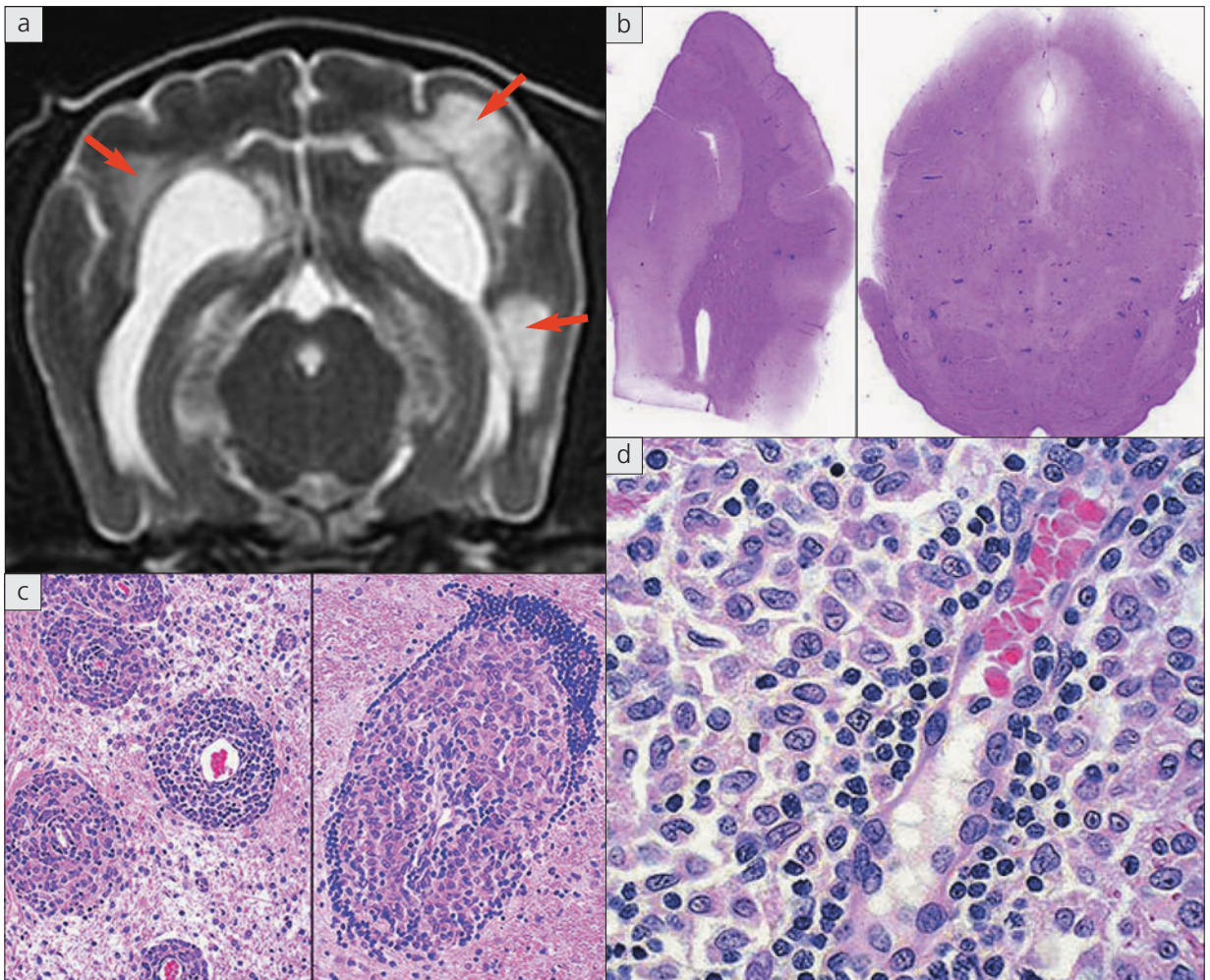
▲ 271 **Disseminated granulomatous meningoencephalitis. (a) Transverse T2-weighted MR image at the level of the midbrain and cerebral hemispheres. Multiple, infiltrative hyperintensities (arrows) are scattered throughout the central white matter. These hyperintense lesions probably represent a combination 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. (From Talarico LR, Schatzberg SJ (2010) Idiopathic granulomatous and necrotizing inflammatory disorders of the canine central nervous system: a review and future perspectives.
J Small Anim Pract 51:138–149, with permission.)**
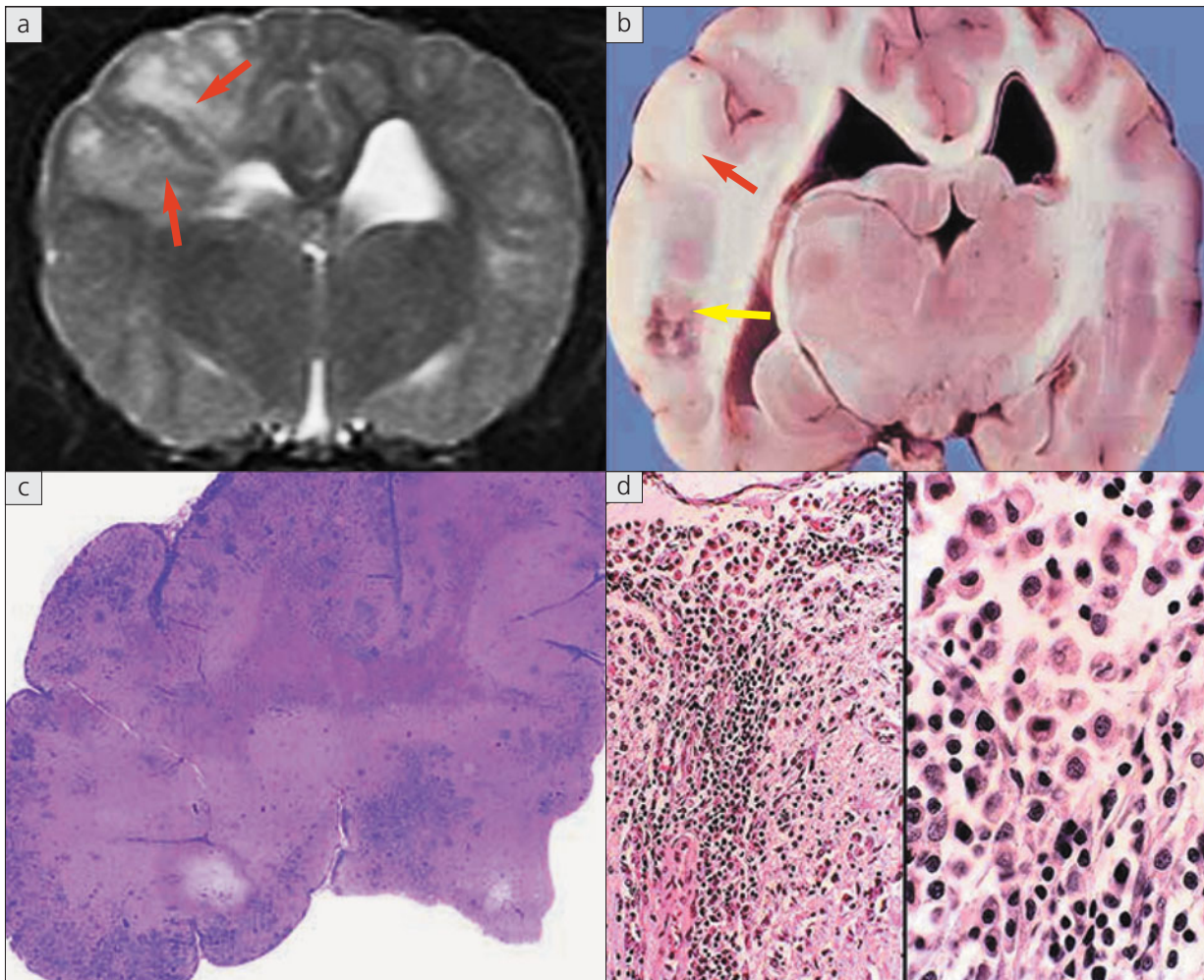
▲ **272** Necrotizing meningoencephalitis. (a) Transverse T2-weighted MR image at the level of the thalamus and cerebral hemispheres. Note the asymmetric, hyperintense, infiltrative lesions affecting the prosencephalon (arrows). The demarcation between grey and white matter is obscured and no evidence of cavitation is seen. (b) Transverse section of the brain at the level of the diencephalon. Inflammation dulls the white matter and characteristically effaces the junction of grey and white matter in the cerebrum (red arrow). Note also the asymmetric swelling, midline shift, slight ventricular enlargement and focal cavitation (yellow arrow). (c) Occipital lobe of a Pomeranian dog. A diffuse infiltrative lesion is present extending from the cortical surface through the grey matter and multifocally entering the white matter. This was a substantially unilateral disease. (d) Cerebral cortex. Meningeal mixed inflammatory infiltrates, which include large and small mononuclear cells and plasma cells. (From Talarico LR, Schatzberg SJ (2010) Idiopathic granulomatous and necrotizing inflammatory disorders of the canine central nervous system: a review and future perspectives. *J Small Anim Pract* 51:138–149, with permission.)
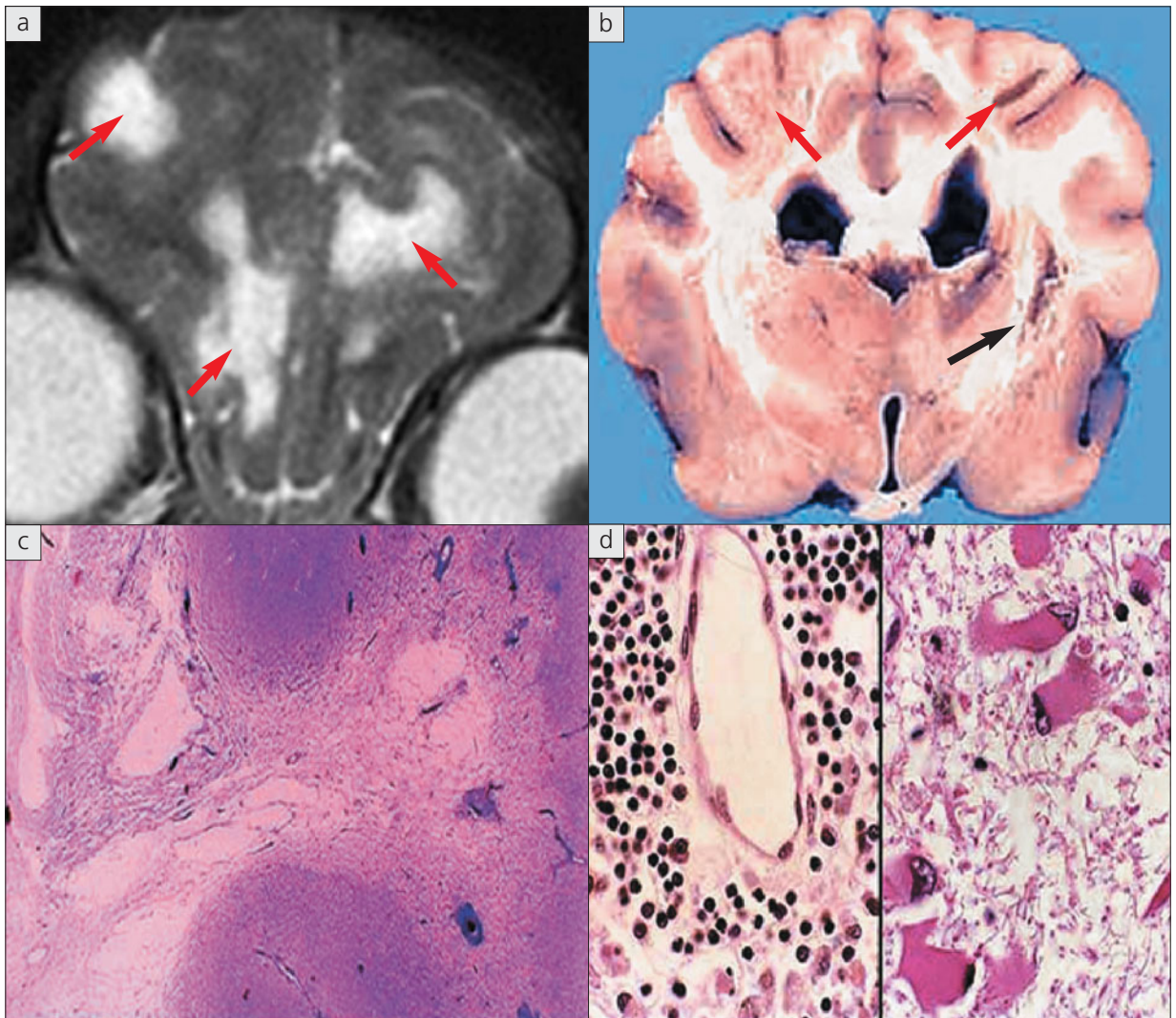
▲ **273** **Necrotizing leucoencephalitis. (a) Transverse T2-weighted MR image at the level of the frontoparietal lobes. Multiple, asymmetric bilateral forebrain lesions, mainly affecting the subcortical white matter, are present (arrows). (b) Asymmetric, cavitating lesions in the corona radiata (red arrows), internal capsule (black arrow) and thalamocortical fibres. (c) Low-magnification view. Corona radiata with intense oedema, dissolution of white matter, early cavitations and residual perivascular cuffing. (d) Corona radiata, high magnification. Left panel: lymphoid and histiocytoid cells cuffing a vessel. Right panel: large reactive astrocytes (gemistocytes). (From Talarico LR, Schatzberg SJ (2010) Idiopathic granulomatous and necrotizing inflammatory disorders of the canine central nervous system: a review and future perspectives. _J Small Anim Pract_ 51:138–149, with permission.)**

NME and NLE are CNS inflammatory disorders with similarly elusive aetiopathogeneses to that of GME. Historically referred to as 'Pug Dog encephalitis' and 'necrotizing encephalitis of Yorkshire Terriers', respectively, these idiopathic MEs have now been reported in many other toy breed dogs. Although notable differences in lesion topography exist between them, the hallmarks of both diseases include non-suppurative ME and variable degrees of cerebral necrosis (**272** page 347, **273**). Clinical signs typically are progressive, reflect the location of cerebral lesions and include seizures, lethargy, circling, visual deficits and ultimately death.

Recently, the authors evaluated pedigree information on a large cohort of Pugs and demonstrated a strong familial inheritance pattern for NME. While this transmission pattern is not surprising, a simple Mendelian inheritance pattern could not be demonstrated. The latter suggests that NME is a multifactorial disorder. Previous screens for viral aetiologies revealed negative results. 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 GME, NME and NLE.

SRMA is a systemic immune disorder characterized by inflammatory, stenosing lesions of the meninges and the associated arteries. The characteristic lesion associated with SRMA is a necrotizing fibrinoid arteritis consisting predominantly of neutrophils and scattered lymphocytes, plasma cells and macrophages. Vasculitis is more common in the leptomeninges of the spinal cord than around the brain, and lesions are occasionally present in the thyroid, heart and mediastinum. Extensive leptomeningeal haemorrhages and meningeal plaques may be apparent grossly. Acute thrombosis of the vasculature may create ischaemic changes.

Idiopathic tremor syndrome is a mild, diffuse, non-suppurative encephalomyelitis, with perivascular cuffing by lymphoplasmacytic mononuclear cells. The lesions affect the CNS diffusely, including the ascending sensory tracts, descending motor tracts and, occasionally, the cerebral and cerebellar hemispheres. CNS myelin is unaffected. The exact aetiopathogenesis is unknown, but an autoimmune disorder affecting neurotransmitter synthesis has been considered. Other potential triggers include pathogens or endogenous epitopes associated with neurotransmitters or cell membrane receptors.

SIGNALMENT AND HISTORY

Infectious meningoencephalomyelitis

Signalment and history may aid in prioritizing infectious MEM over idiopathic MEM. For example, an inappropriate vaccination history may raise the index of suspicion for CDV or rabies MEM. Similarly, a history of travel to endemic areas or recent tick exposure may suggest fungal or rickettsial disease, respectively. The most common age group in which FIP occurs in cats is between 6 months and 2 years of age, followed by geriatric cats >14 years of age. There are no breed predispositions for FIP; however, intact male cats and those in stressful environments (e.g. catteries) may be at an increased risk.

Idiopathic meningoencephalomyelitis

Breed and age are particularly important for the recognition of the idiopathic MEMs. GME is most common in females and toy and terrier breeds, but both sexes and all breeds may be affected. For GME, the mean age of onset of neurological signs is 5–6 years (range: 6 months to 12 years). NME and NLE have been reported in various toy breeds including the Pug, Maltese, Chihuahua, Yorkshire Terrier, Pekingese, West Highland White Terrier, Boston Terrier, Japanese Spitz and Miniature Pinscher. The age of onset of neurological signs associated with NME varies from 6 months to 7 years of age and most commonly occurs in young dogs, with a mean age of 29 months. NLE typically manifests between 4 months and 10 year of age, with a mean age of onset of 4.5 years.

SRMA may occur in any breed of dog, although young Beagles, Boxers, Bernese Mountain Dogs, German Short-haired Pointers and Nova Scotia Duck Tolling Retrievers are overrepresented. The age of onset of neurological signs associated with SRMA is commonly between 6 and 18 months, with a range from 4 months to 7 years.

Idiopathic tremor syndrome affects predominately small breed dogs, most commonly Maltese, Cocker Spaniels and West Highland White Terriers. Affected dogs typically present between 1 and 5 years of age, may be any colour (although often are white) and typically weigh <15 kg.

CLINICAL PRESENTATION

General meningoencephalomyelitis

The clinical presentation of infectious or idiopathic MEM is variable, as any part of the neuraxis may be affected by inflammation. MEM may be focal, multifocal or diffuse in nature and patients often present with symmetric neurological signs (**274**). As mentioned previously, clinical signs of encephalomyelitis reflect the location of the lesion(s). Animals with meningitis may be presented for discomfort in the acute stage of disease, but may progress to manifest obvious neurological deficits in the later stages (if the underlying neuroparenchyma becomes inflamed).

Infectious meningoencephalomyelitis

Neurological signs caused by infectious agents are extremely variable and are dependent on the neuroanatomical location of the lesion(s). Although the neurological signs alone should not form the basis of a diagnosis of infectious MEM, some infectious agents cause 'classic' neurological signs. For example, CDV often produces generalized flexor spasms of the muscles of the limbs, neck and/or masticatory muscles, so-called CDV myoclonus. Rabies infection may cause 'paralytic (dumb)' or 'furious' variants of disease, caused by ascending LMN paresis and limbic system involvement, respectively. Toxoplasmosis and neosporosis often affect puppies with a combination of LMN signs and MEM. Cats with CNS FIP typically are presented for acutely progressive, multifocal to diffuse neurological signs including seizures, behavioural abnormalities, cerebellovestibular signs, GP ataxia and various degrees of fore- and hindlimb paresis to paralysis.

The typical presentation for bacterial meningitis and/or CNS abscesses is an acutely progressive condition with variable neurological deficits. Clinical signs of meningitis include cervical hyperaesthesia, low head carriage and pain on palpation. In addition, vomiting, bradycardia and seizures may occur. CNS abscesses often lead to a focal localization; however, a multifocal localization may be present with multiple abscesses. If an infectious MEM is suspected, systemic signs should be evaluated carefully. Infectious CNS diseases are associated with systemic signs more frequently than the idiopathic MEMs, including:
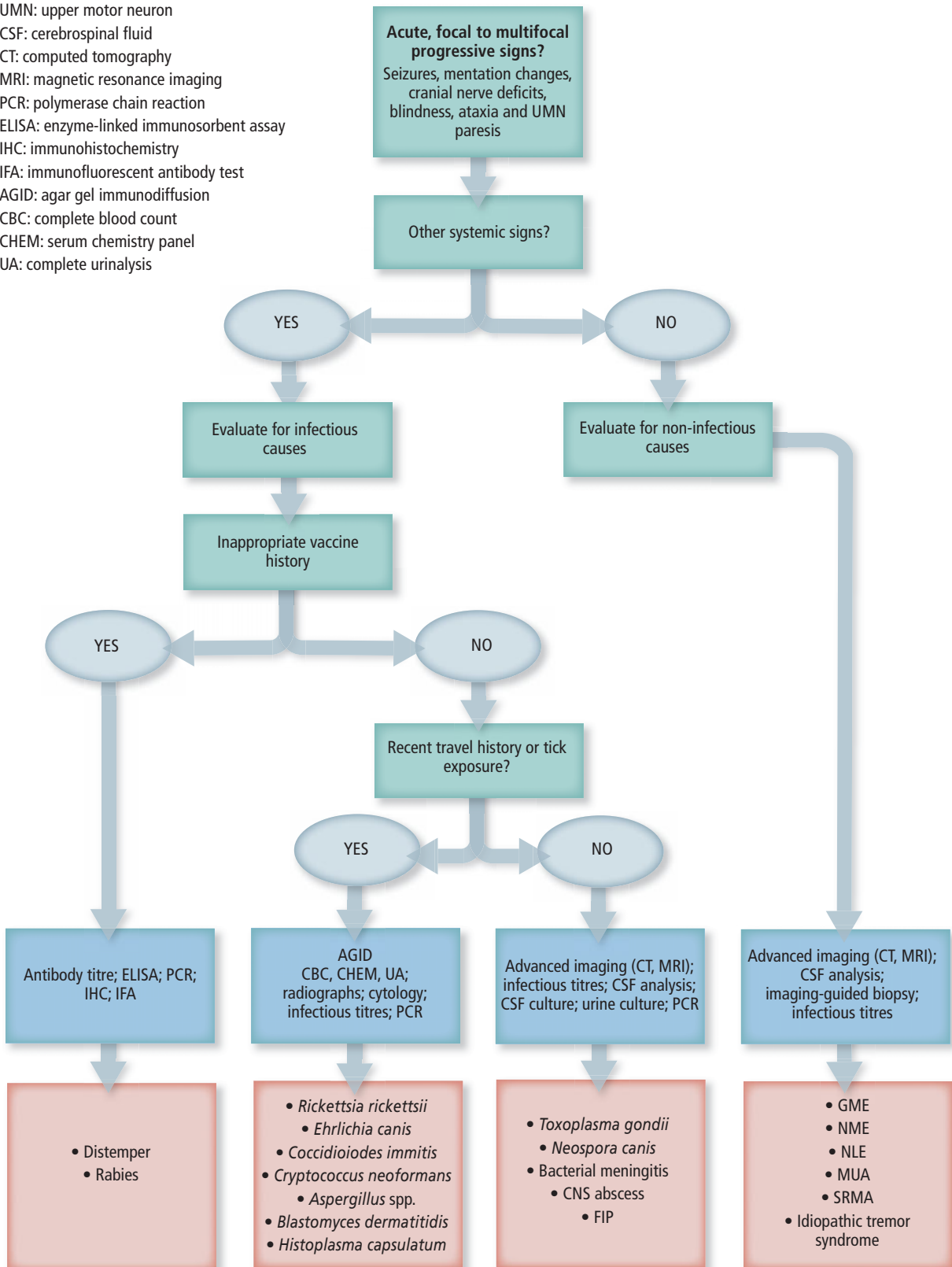
- A source or foci (e.g. liver abscess, pneumonia, bacterial endocarditis) or evidence of direct extension from the eyes, ears or nasal cavity with bacterial MEM and bacterial abscesses.
- Pulmonary, gastrointestinal, ocular and integumentary abnormalities with CDV infection.
- Focal haemorrhages (secondary to vasculitis), fundic abnormalities (haemorrhage, exudate), fever, peripheral oedema, thrombocytopenia, lymphadenopathy, renal disease and arthropathy with rickettsial infections.
- Multisystem involvement, including pulmonary, skin, musculoskeletal, ocular, and internal organ involvement, with fungal and protozoal disease.
- Fever, hyperglobulinaemia and chorioretinitis with FIP.

Idiopathic meningoencephalomyelitis

As with the infectious MEMs, the neurological signs of the idiopathic disorders tend to be reflective of the neuroanatomical locations of the lesion(s). Disseminated GME often presents as an acutely progressive, multifocal neurological disease that may be fatal if left untreated. Neurological deficits referable to the caudal cranial fossa (vestibulocerebellar signs) and cervical spinal cord, in addition to seizures and visual deficits, have been reported most frequently. Neurological signs associated with the uncommon, focal form of GME may be acute or slowly progressive and they are suggestive of a single space-occupying mass lesion. Forebrain signs were reported most frequently with focal GME in one study, although the brainstem or spinal cord may be affected. The ocular form of GME manifests with an acute onset of visual impairment, variable pupillary changes (commonly dilated and unresponsive), variable degrees of optic nerve oedema and occasionally chorioretinitis, especially in the non-tapetal fundus. Dogs with ocular GME may concurrently have, or progress to develop, disseminated CNS lesions.

▶ **274** **Algorithm for diagnosis of acute meningoencephalomyelitis.**

UMN: upper motor neuron
CSF: cerebrospinal fluid
CT: computed tomography
MRI: magnetic resonance imaging
PCR: polymerase chain reaction
ELISA: enzyme-linked immunosorbent assay
IHC: immunohistochemistry
IFA: immunofluorescent antibody test
AGID: agar gel immunodiffusion
CBC: complete blood count
CHEM: serum chemistry panel
UA: complete urinalysis

Acute, focal to multifocal progressive signs?
Seizures, mentation changes, cranial nerve deficits, blindness, ataxia and UMN paresis

Other systemic signs?

YES — NO

Evaluate for infectious causes

Evaluate for non-infectious causes

Inappropriate vaccine history

YES — NO

Recent travel history or tick exposure?

YES — NO

Antibody titre; ELISA; PCR; IHC; IFA

AGID
CBC, CHEM, UA; radiographs; cytology; infectious titres; PCR

Advanced imaging (CT, MRI); infectious titres; CSF analysis; CSF culture; urine culture; PCR

Advanced imaging (CT, MRI); CSF analysis; imaging-guided biopsy; infectious titres

- Distemper
- Rabies

- *Rickettsia rickettsii*
- *Ehrlichia canis*
- *Coccidioiodes immitis*
- *Cryptococcus neoformans*
- *Aspergillus* spp.
- *Blastomyces dermatitidis*
- *Histoplasma capsulatum*

- *Toxoplasma gondii*
- *Neospora canis*
- Bacterial meningitis
- CNS abscess
- FIP

- GME
- NME
- NLE
- MUA
- SRMA
- Idiopathic tremor syndrome

Dogs with both NME and NLE commonly manifest forebrain signs due to the predominance of lesions in the prosencephalon. NLE may also cause mid to caudal brainstem signs. The signs associated with NME and NLE typically are rapidly progressive and most commonly include seizures, depression, circling, vestibulocerebellar signs, visual deficits and ultimately death.

Clinical signs with SRMA are characterized by episodes of profound cervical hyperaesthesia, depression and pyrexia. Two forms of SRMA exist, i.e. the 'classic' acute form and the chronic protracted form. In acute SRMA, dogs most commonly present with hyperaesthesia along the vertebral column, cervical rigidity, stiff gait and fever. Affected animals often manifest a hunched posture with profound guarding of the head and neck, sometimes mimicking a cervical intervertebral disc protrusion. Dogs may be in so much pain that any manipulation elicits a painful response. The chronic form of SRMA most often occurs following relapses of acute disease and/or inadequate treatment. Involvement of the motor and proprioceptive systems may lead to variable degrees of paresis and ataxia. Other neurological signs, such as menace deficits, anisocoria or strabismus, may occur with severe disease.

Idiopathic tremor syndrome typically causes fine tremors affecting all four limbs, the head and sometimes the eyes. The tremors tend to worsen with exercise, stress and excitement, but disappear with sleep. Neurological examination typically is normal, although absent menace responses, nystagmus, dysconjugate eye movements, head tilt, nondescript ataxia, hypermetria, body swaying, varying degrees of paresis and, rarely, seizures have been reported. Neurological signs manifest sporadically, often progress over several days and typically remain static if untreated. Clinical complications associated with prolonged tremors include severe hyperthermia, hypoglycaemia, dehydration and anorexia.

Although the idiopathic MEMs are restricted to the CNS, the severity and location of the CNS lesions occasionally produce profound systemic changes (e.g. autonomic changes with brainstem lesions). Due to the acute, progressive nature of the majority of the conditions causing MEM, dogs and cats often present for emergency evaluation, therefore it is essential to formulate an accurate differential diagnosis in order to perform the correct diagnostic investigations.

DIFFERENTIAL DIAGNOSIS

Metabolic derangements; congenital anomalies (decompensating hydrocephalus, Chiari-like malformation); tumours of the meninges (histiocytosis, lymphoma, meningioma); intervertebral disc disease; atlantoaxial subluxation; cerebrovascular accident; head trauma; mycotoxin and neurotoxin ingestion (for idiopathic tremor syndrome and occasionally disseminated GME).

DIAGNOSIS

Key diagnostic tests for MEM include molecular and advanced imaging diagnostics (*Table 79*).

General meningoencephalomyelitis
The differential diagnosis for dogs presented for an acute onset of multifocal CNS signs includes decompensating congenital abnormalities, metabolic derangements, infectious and idiopathic MEM, neoplasia and toxin exposure. Differentiating these disorders may be challenging. Diagnostic testing typically includes a minimum database (CBC, chemistry panel and urinalysis), survey radiographs of the thorax (+/- abdominal ultrasound) to rule out systemic disease and metastatic neoplasia, advanced cross-sectional imaging via CT or MRI and CSF collection and analysis. Although more often utilized for suspected brain tumours, CT-guided brain biopsy and histopathological evaluation of brain tissue may be considered in cases of suspected ME.

CSF analysis is a key component of the neurodiagnostic work-up and typically includes cytological evaluation, differential cell counts and TP measurement (*Table 80*). While pleocytosis is commonly present in cases of MEM, cytology rarely provides definitive differentiation among idiopathic, infectious and neoplastic disorders. On occasion, bacteria, fungi, protozoa or parasites may be identified on microscopic examination of CSF (see Chapter 5); however, this is extremely rare. One must be especially cautious not to 'overinterpret' the CSF profile. For example, in confirmed cases of MEM, CSF analysis occasionally reveals no abnormalities. Despite its limitations, the CSF WBC differential may help the clinician to narrow down the differential diagnosis, especially when combined with cross-sectional imaging of the CNS.

Table 79 Diagnostic tests for meningoencephalomyelitis

DISEASE	DIAGNOSTIC TESTS
Infectious MEM	
Bacterial meningitis	CSF analysis/culture; eubacterial PCR; urine culture
CNS abscess	CSF analysis/culture; eubacterial PCR; urine culture; CT/MRI
Canine distemper virus	PCR of CSF, urine or conjunctival scraping; IHC of skin biopsy; CSF and serum IgM and IgG ratios
FIP	CSF analysis; RT-PCR of CSF or cavitary fluid; CT/MRI, biopsy
Rickettsia rickettsii	Antibody titres; CSF analysis; PCR
Ehrlichia canis	Antibody titres; CSF analysis; PCR
Rabies virus	IFA – postmortem examination
Toxoplasma/Neospora	Antibody titres; CSF analysis; PCR
Cyrptococcus neoformans	Latex agglutination antigen test; CSF analysis/culture
Coccidioides immitis	Complement fixation or AGID (antibody); CSF analysis/culture
Blastomyces dermatitidis	Urine antigen assay
Aspergillus spp.	Latex agglutination antigen test
Parasitic MEM	
Dirofilaria immitis	Antigen ELISA, antibody titres (cat), microfilaria identification
Cuterebra larva	Advanced imaging, postmortem examination
Idiopathic MEM	
GME, NME, NLE, MUA	CSF analysis and lymphoma PCR; CT/MRI; biopsy
SRMA	CSF analysis; CSF culture to rule out infection; CT/MRI
Idiopathic tremor syndrome	CSF analysis; CT/MRI

In both acute and chronic SRMA, blood work may show a neutrophilia with a left shift, an increased erythrocyte sedimentation rate and an elevated alpha2-globulin fraction. The majority of affected dogs have elevated IgA levels in both the CSF and serum, a finding that is probably secondary to dysregulation of the immune system. Elevated serum and CSF IgA levels help differentiate SRMA from other idiopathic and infectious canine meningoencephalitides; however, elevated IgA levels may be associated with primary or secondary inflammation. Elevated IgM and/or IgG levels in the CSF have also been documented. More recently, acute phase proteins (APPs), including C-reactive protein (CRP) and alpha2-macroglobulin, have been shown to be elevated consistently in the serum of dogs with SRMA. However, elevation of APPs is not pathognomonic for the disorder and other systemic inflammatory diseases should be included in the differential diagnosis when it is present. Once SRMA has been confirmed, elevated CRP serum concentrations may be used reliably to monitor response to therapy, rather than repeated CSF collection and analysis.

The presence of anti-astrocytic and glial fibrillary acid protein (GFAP) autoantibodies has been documented in the CSF of affected NME dogs. However, similar antibody levels occur in the CSF of dogs with GME, brain tumours and even some clinically normal dogs. The diagnostic utility of autoantibodies in monitoring response to therapy is limited, since anti-GFAP autoantibodies can even be detected during clinically successful immunosuppressive therapies.

While CT may have diagnostic utility in some cases of inflammatory brain disease, MRI is the gold standard neuroimaging modality for MEM. MRI 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 (e.g. NME versus NLE) and presence or absence of necrosis (e.g. NME versus GME) may be imaging features that help direct a presumptive antemortem diagnosis. In a recent MRI study, 17/18 Pug dogs with NME had forebrain lesions, with 16/18 having a lesion in the parietal, temporal and occipital lobes. Also, all the Pugs

had asymmetric lesions in both the grey and white matter of the neuroparenchyma. MRI also has several advantages over CT as it provides excellent anatomical 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, when coupled with CSF analysis it may help to provide evidence of MEM.

Infectious meningoencephalomyelitis

Traditional techniques to diagnose infectious CNS diseases in dogs and cats include CSF analysis, microbial culture, serological antibody titres, immunohistochemistry (IHC), immunofluorescent antibody (IFA), ELISA and agar gel immunodiffusion (AGID). Identification of infectious organisms on cytology is rare; microbial culture should be considered in cases with systemic signs, potential sources of infection (e.g. otitis media/interna) and CBC/biochemistry abnormalities (e.g. fever, leucocytosis). CSF fungal culture may also be considered in cases with concurrent systemic signs (skin, bone, ocular, internal organ involvement).

Serology and/or PCR should be performed when infectious agents are suspected to be the cause of MEM.

Table 80   CSF analysis findings in canine and feline CNS disease

	TOTAL PROTEIN LEVEL	NUCLEATED CELL COUNT	CYTOLOGY
Viral meningoencephalitis (CDV and other)	Normal–markedly elevated	Normal–moderate pleocytosis	Mononuclear
Bacterial meningoencephalitis	Mildy–markedly elevated	Moderate–marked pleocytosis	Predominantly neutrophilic
Protozoal meningoencephalitis	Mildy–markedly elevated	Moderate pleocytosis	Mixed, occasionally eosinophilic
Fungal meningoencephalitis	Markedly elevated	Moderate–marked pleocytosis	Mixed, occasionally eosinophilic
CNS parasites	Mildy–markedly elevated	Mild–moderate pleocytosis	Mixed, often eosinophilic
Granulomatous meningoencephalitis	Mildy–markedly elevated	Normal–marked pleocytosis	Variable: mononuclear, mixed, occasionally eosinophilic
Eosinophilic meningoencephalitis	Mildy–markedly elevated	Mild–marked pleocytosis	Eosinophils
Steroid-responsive meningitis–arteritis	Mildy–markedly elevated	Moderate–marked pleocytosis	Acute: neutrophilic; Chronic: mononuclear
Necrotizing meningoencephalitis, or necrotizing leukoencephalitis	Mildy elevated	Mild–marked pleocytosis	Mononuclear
Feline infectious peritonitis infection	Markedly elevated	Moderate–marked pleocytosis	Mixed, occasionally eosinophilic
Neoplasia	Variable: normal–markedly elevated	Variable: normal–marked pleocytosis	Variable: mononuclear, neutrophilic (e.g. meningioma), occasionally eosinophilic or neoplastic cells (e.g. lymphosarcoma)
Degenerative disorders	Normal–moderately elevated	Normal	—
Necrosis	Normal–markedly elevated	Variable: normal–marked pleocytosis	Mixed pleocytosis (often neutrophilic)
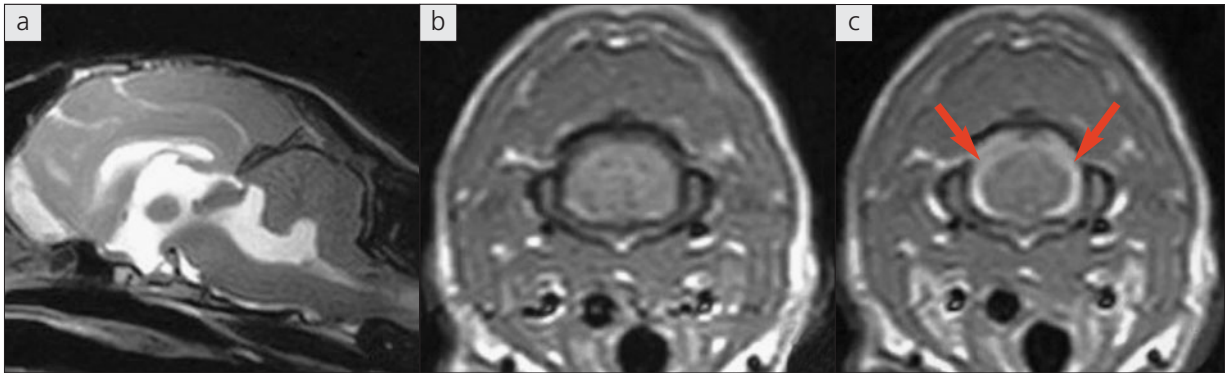
▲ **275** **(a) Sagittal T2-weighted image of the brain of an 8-month-old cat with the CNS form of FIP. There is marked dilatation of the 3rd and 4th ventricles, with secondary dorsal displacement of the cerebellum and cerebellar vermal herniation through the foramen magnum. The proximal part of the cervical spinal cord appears swollen and hyperintense. (b) Transverse T1-weighted and (c) T1-weighted post-contrast images of the spinal cord at the level of C1. There is marked thickening and contrast enhancement of the meninges surrounding the spinal cord (arrows), which probably accounts for the secondary obstructive hydrocephalus. FIP is a surface-related disease affecting mostly the leptomeninges and ependymal lining of the CNS. (Photo courtesy Laurent Garosi)**

IgM and IgG antibodies reflect acute and chronic infections, respectively, and can be evaluated in the serum and/or CSF. Although positive antibody titres reflect direct exposure to an organism, a positive titre does not confirm active infection. Serology results must be interpreted in light of the patient's signalment, history, neurological and systemic signs, CSF analysis and imaging results. Serum and CSF serology and PCR may be pursued for *Toxoplasma gondii* (IgG and IgM ELISA, PCR), *Neospora caninum* (IgG indirect IFA, PCR), *Ehrlichia* spp. (IgG indirect IFA, PCR) and *Rickettsia rickettsii* (IgG IFA, PCR). AGID panels and panfungal PCR are available for *Cryptococcus*, *Blastomyces*, *Coccidioides*, and *Histoplasma* spp. Eubacterial PCR detection of 16S ribosomal subunits is currently being investigated.

Biopsy and IHC are required for the definitive diagnosis of FIP. However, a presumptive antemortem diagnosis can be achieved with CSF analysis and MRI. CSF analysis typically reveals protein levels of 2 g/l (200 mg/dl) or greater and a moderate to marked neutrophilic pleocytosis. MRI may reveal periventricular contrast enhancement, ventricular dilatation and/or hydrocephalus (**275**). Reverse transcription PCR of FIP virus in infected macrophages has been reported; however, false positives may occur in healthy cats .

Since CSF and MRI findings are highly variable with CDV infection, diagnostic techniques with greater specificity must be utilized. Immunohistochemical testing for CDV antigen on biopsies of nasal mucosa, footpad epithelium and the haired skin of the dorsal neck has been reported to be a relatively sensitive and specific test. Similarly, reverse transcription PCR applied to RNA extracted from whole blood, urine, CSF, tonsilar or conjunctival specimens is a sensitive and specific assay.

Idiopathic meningoencephalomyelitis

A definitive antemortem diagnosis of the specific variants of idiopathic MEM is challenging, since histopathological confirmation is required (**276**). In most cases a presumptive antemortem diagnosis is achieved via a multimodal approach that includes assessment of case signalment, neurological signs and neuroanatomical localization, CSF analysis, cross-sectional imaging of the CNS and negative infectious disease testing. The antemortem diagnosis is often complicated by an overlap in the neurodiagnostic profiles (especially between GME and the necrotizing encephalitides). Therefore, the terminology meningoencephalitis of unknown aetiology (MUA) may be preferable on an antemortem basis in cases of idiopathic ME where histopathology is lacking.

The following points regarding CSF analysis (see also *Table 80*) and cross-sectional imaging may help with presumptive diagnoses of the idiopathic MEMs:

- The CSF profiles for GME, NME, NLE and chronic SRMA overlap, with a mononuclear (lymphocytes, monocytes) pleocytosis and TP elevations being most common.
- The CSF profile for acute SRMA is typified by a neutrophilic pleocytosis, TP elevation and elevated IgA (CSF and serum).
- The CSF profile for idiopathic tremor syndrome is typified by a lymphocytic pleocytosis and TP elevation.
- Although not specific for GME, the most common MRI findings for the disseminated form include multiple hyperintensities on T2-weighted or FLAIR sequences scattered throughout the CNS white matter. These lesions typically assume an infiltrative appearance and have irregular margins.
- Despite the predilection of the GME for white matter, MRI lesions are often distributed throughout both grey and white matter. Compared with cerebral parenchyma, the lesions are hyperintense on T2-weighted images, variable intensity on T1-weighted images and have variable degrees of contrast enhancement. Vasogenic oedema in the white matter is commonly appreciable on T2-weighted and T1-weighted images as hyper- and hypointense to cerebral parenchyma, respectively.
- Both focal and disseminated forms of GME may be associated with contrast enhancement of the parenchyma and meninges on CT, and mass effect
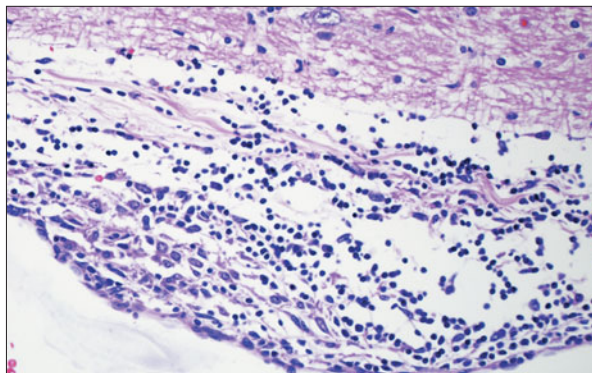
▲ **276** Histopathology of the brain and meningeal tissue from a canine case of GME (× 20), which demonstrates the cellular accumulation within the meninges often evident in these cases. (Photo courtesy Victoria Watson)

may be observed as displacement of surrounding brain tissue. Some lesions may be associated with hypoattenuating vasogenic (white matter) oedema.
- The focal form of GME may be identified on CT or MRI as a nonspecific, single, space-occupying mass lesion.
- In ocular GME, the optic nerves may be hyperintense on T2-weighted images and may show contrast enhancement on T1-weighted images. The optic chiasm also may appear enlarged, reflecting the gross pathology.
- Mild NME, infectious ME, CNS lymphosarcoma and glial and metastatic neoplasms may present with similar clinical and MRI findings to disseminated GME, and discriminating among these differentials may be challenging unless tissue biopsy is obtained.
- 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. Loss of grey/white matter demarcation also may be discernible. 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 pros-encephalic lesions mainly affecting the subcortical white matter have been described. The NLE lesions are hyperintense on T2-weighted and FLAIR images and often include multiple cystic areas of necrosis. These lesions are hypointense or isointense on T1-weighted images, and contrast enhancement is variable.
- Although leptomeningeal enhancement may be appreciated on CT or MRI with SRMA or idiopathic tremor syndrome, cross-sectional imaging typically is normal for both disorders.

MANAGEMENT

Infectious meningoencephalomyelitis

Treatment of bacterial meningitis and CNS abscesses necessitates the selection of an antibiotic that effectively crosses the blood–brain/CSF barrier. Antibiotic selection should be based on culture and sensitivity results if available. Empirical antibiotics should initially be given intravenously for 2–3 days to reach therapeutic levels in a timely manner. Antibiotic choices include trimethoprim sulphonamide (30–60 mg/kg q24h) and metronidazole (10–15 mg/kg q12h). Other choices include third-generation cephalosporins and fluoroquinolones such as enrofloxacin (5–10 mg/kg q24h). Antibiotics should be continued for 3–4 weeks after clinical signs have resolved. Intravenous dexamethasone (0.05–0.1 mg/kg q24h) can be given for the first 24–48 hours to decrease vasogenic oedema. Increased ICP may be seen with large CNS abscesses (see below for treatment of increased ICP). Abscesses of the CNS may be refractory to treatment due to the fibrous capsule. Surgical decompression by craniotomy, burr holes or laminectomy may be indicated in cases of cranial subdural or spinal epidural empyema.

To date, there is no definitive treatment for viral ME. Supportive treatment and broad-spectrum antibiotics are given to prevent secondary bacterial infections in cases of CDV and FIP infection. Anti-inflammatory corticosteroids may reduce inflammation in dogs or cats with any suspected viral ME. Euthanasia is recommended for all animals with a history and clinical signs supportive of rabies infection. In addition, rabies is a notifiable disease in some countries and appropriate measures to inform the relevant authorities should be taken.

For toxoplasmosis or neosporosis, clindamycin (10–25 mg/kg IV initially, then PO q12h for 3–4 weeks) may lead to a favourable outcome. Trimethoprim sulphonamide (15 mg/kg PO q12h) in combination with pyrimethamine (1 mg/kg/day PO) may also be effective. Folinic acid or brewers yeast supplementation should be considered (5 mg/dog q24h) in animals receiving this latter therapy. However, bradyzoite cysts may not be affected by antibiotics, resulting in disease recrudescence during periods of immunosuppression, with possible initiation of clinical signs. Rickettsial organisms should be treated with doxycycline (5–10 mg/kg q12h for 4–6 weeks). Fungal MEM may be treated with voriconazole (40–60 mg/kg PO q24h). Cryptococcal infections are often treated with a combination of fluconazole (2.5–5.0 mg/kg PO) and amphotericin B (0.5–0.8 mg/kg SC [diluted in 0.45% NaCl with 2.5% dextrose]) 2–3 times per week (**277**, next page).

Anti-inflammatory doses of corticosteroids can be given in some cases of infectious MEM in which vasogenic oedema and/or an immune-mediated component of the disease process is present. Dexamethasone (0.05–0.1 mg/kg IV q24h for the first 24–48 hours) followed by prednisolone (0.5–1.0 mg/kg PO q24h for 1–2 weeks) can be used in the acute setting of infectious MEM.

Idiopathic meningoencephalomyelitis (GME, NME, NLE, MUA)

The primary therapy for idiopathic MEM is immuno-suppression with corticosteroids and secondary immunosuppressive agents.

Once an infectious aetiology has been ruled out and a presumptive or definitive diagnosis of idiopathic MEM reached, treatment should be instituted as soon as possible. The patient should initially be stabilized if neurological derangements have produced respiratory or cardiovascular abnormalities (e.g. seizures or brainstem lesions causing secondary autonomic changes). Supplementary oxygen should be given for hypoxaemia and crystalloid/colloid support for perfusion and hypotension, as needed. Once systemic parameters are stabilized, therapy should be instituted (1) to prevent neurological deterioration, (2) to halt the immune response with immunosuppressive therapy and (3) to provide support for a recumbent patient if needed (**278**, page 359).

▶ **277** **Treatment algorithm for infectious MEM.**

INFECTIOUS MEM

Monitor vital parameters (airway, breathing, circulation)

Intracranial stabilization (monitor neurological status)

Antimicrobial therapy

Seizures

Diazepam 0.5–2.0 mg/kg
CRI 0.1–0.5 mg/kg/hour
Midazolam 0.06–0.3 mg/kg IV
Propofol bolus 1–2 mg/kg IV
CRI 0.1–0.6 mg/kg/minute

Bacterial meningitis/ CNS abscess

Protozoal

Rickettsial

Fungal

CDV and FIP

Chloramphenicol
40–50 mg/kg q8h
Metronidazole
10–15 mg/kg q12h
Enrofloxacin
5–10 mg/kg q24h
Trimethoprim–
sulphonamide
30 mg/kg q12h
Third-generation
cephalosporins

Clindamycin
10–25 mg/kg q12h
Trimethoprim–
sulphonamide
15 mg/kg q12h

Doxycycline
5–10 mg/kg q12h

Voriconazole
40–60 mg/kg q24h
Voriconazole >>>
itraconazole for
Aspergillus spp.
Fluconazole 2.5–5.0
mg/kg q24h and
amphotericin B
0.5–0.8 mg/kg q24h
for 2–3 times/week for
Cryptococcus spp.

Broad-spectrum
antibiotic, supportive
Consider prednisone
0.5–1 mg/kg/day

▶ **278** **Treatment algorithm for GME, NME, NLE and MUA.**

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                          ┌───────────────────────┐
                          │   IDIOPATHIC MEM       │
                          │ (GME, NME, NLE, MUA)   │
                          └───────────────────────┘
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| Monitor vital parameters (airway, breathing, circulation) | Intracranial stabilization (monitor neurological status) | Immunosuppressive therapy | Supportive care Recumbency, urinary and faecal management |

| Imaging or clinical evidence of raised ICP | Seizures | | |

Mannitol 0.5–2.0 g/kg over 15 minutes (crystalloid fluid replacement first) followed by 0.5–1 mg/kg furosemide IV
7% hypertonic saline 1–2 ml/kg IV over 5–10 minutes in normotensive animal
7% hypertonic saline 4 ml/kg IV over 5–10 minutes in hypotensive animal

Diazepam 0.5–2.0 mg/kg CRI 0.1–0.5 mg/kg/hour
Midazolam 0.06–0.3 mg/kg IV
Propofol bolus 4–8 mg/kg IV CRI 1–5 mg/kg/hour

Corticosteroids (prednisone) 2–4 mg/kg/day
Cytosine arabinoside 200–600 mg/m^{2}SC or IV over 24 hours

Preventing neurological deterioration

If seizures are present, diazepam or midazolam may be given. (For control of emergency seizures see Chapter 23.) If neurological status progressively worsens and increased ICP is suspected, mannitol may be given through an in-line filter. Some clinicians recommend mannitol dosing every 30 minutes until the desired effect has been achieved. Intravenous furosemide may also be given following mannitol administration. The patient must be adequately hydrated before mannitol is given in order to prevent hypovolaemia and potential renal damage. An alternative to mannitol is hypertonic saline. (See Chapters 20 and 26 for management of elevated ICP.)

Halting the immune response with immunosuppressive therapy

At present, immunosuppression is the mainstay of therapy for MUA. Most clinicians treat MUA with corticosteroids (prednisone or dexamethasone). In a large study of dogs with GME, radiation therapy appeared to be the only independent predictor of patient survival. However, these results may be biased, as patient inclusion was based on only necropsied GME dogs. Depending on the severity of signs and the index of suspicion for infectious disease, some specialists will initiate therapy with anti-inflammatory steroids (prednisone, 0.5–1.0 mg/kg PO q24h) and await serology and PCR results for screening of regional infectious diseases.

If the index of suspicion is extremely high for idiopathic inflammatory disease (e.g. Pug with MRI lesions consistent with NME), the authors immediately 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 use secondary immunomodulatory agents on review of negative serology and PCR results.

In a clinical setting, steroid monotherapy may resolve signs associated with MUA in some dogs, but insufficiently or only transiently provide 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 additional immunomodulatory drugs to treat MUA (e.g. cytosine arabinoside [CA], 50 mg/m^2 SC q12h for 2 days [see *Table 81*]; procarbazine, 25–50 mg/m^2 PO q24h; cyclosporine, 5–10 mg/kg PO q12h; azathioprine, 2 mg/kg PO q24h; mycophenolate, 10–20 mg/kg PO q12h; and leflunomide, 2–4 mg/kg PO q24). In a recent study, patient survival times and adverse effects were compared between a prednisone/vincristine/cyclophosphamide protocol and a prednisone/CA protocol. There was no significant difference between survival times between the two groups. Adverse effects were seen more often in the cyclophosphamide group. The authors commonly use CA as an adjunctive therapy for MUA in combination with prednisone using the following protocol:

- 1.5 mg/kg q12h for 3 weeks;
- 1.0 mg/kg q12h for 6 weeks;
- 0.5 mg/kg q12h for 3 weeks;
- 0.5 mg/kg q24h for 3 weeks;
- 0.5 mg/kg q48h indefinitely (may reduce to 0.25 mg/kg q48h).

Intravenous rescue CA protocols (IV CRI at 200 mg/m^2 over 48 hours) have been described for the initial treatment of severe idiopathic MEM. The authors have also used a higher intravenous dose regimen (600 mg/m^2 over 24–48 hours), which seems to be useful for severe relapses. It is recommended that intravenous rescue CA protocols are used in severely affected dogs.

Table 81   Cytosine arabinoside regimen for idiopathic meningoencephalomyelitis

Intervals between treatment*	Dosages given on consecutive days	Number of treatments
3 weeks apart	50 mg/m^2 SC q12h x 2 days	4
4 weeks apart	50 mg/m^2 SC q12h x 2 days	4
5 weeks apart	50 mg/m^2 SC q12h x 2 days	4
6 weeks apart	50 mg/m^2 SC q12h x 2 days	Indefinitely

Intervals between doses can be adjusted based on clinical response and occasionally repeat CSF analysis and MRI.

* Treatment interval should only be extended if the patient remains in clinical remission. If clinical signs recur, the last effective treatment interval should be used indefinitely. At the 6-week stage, an attempt to take the dog off CA can be made based on clinical response.

Treatment is monitored by clinical response and regression of neurological deficits and occasionally repeated CSF analysis and MRI. In our experience, side-effects have been minimal and dogs with MUA have a fair long-term prognosis with combined CA/prednisone therapy. However, CBCs are evaluated 10–14 days after the first dosing regimen, then every 2–3 months to monitor myeloid cell lines.

Providing support for a recumbent patient

Recumbent patients need to be properly managed to prevent bed sores and urine scald. Ideally, the recumbency of the patient and appropriate urinary and faecal management need to be addressed every 4–6 hours. Urine and faeces must be cleaned off the patient as soon as possible in order to prevent dermatitis. Occasionally, recumbent and, sometimes, demented patients may need fluid therapy to support base fluid requirement and compensate for corticosteroid-induced polyuria.

Idiopathic meningoencephalomyelitis (presumptive SRMA and idiopathic tremor syndrome)

Immunosuppressive doses of corticosteroids form the cornerstone of therapy for SRMA and idiopathic tremor syndrome. For SRMA, the following protocol has been recommended for a minimum of 6 months:

- Prednisone (2 mg/kg PO or IV initially q12h). After 2 days the dose is reduced to 1 mg/kg PO q12h for 1–2 weeks, followed by 0.5 mg/kg PO q12h.
- Dogs are re-examined every 4–6 weeks; CSF analysis and haematology can be repeated every 4–6 weeks.
- When clinical signs and/or CSF are normal, the dose is reduced by half until a dose of 0.5 mg/kg q48–72h is reached.
- Treatment is stopped 6 months after clinical examination and CSF evaluation are normal.
- For chronic or refractory cases, other immunosuppressive drugs, such as azathioprine (1.5–2.0 mg/kg PO q48h), may be used in combination with steroids (e.g. alternating each drug every other day).

The majority of dogs with idiopathic tremor syndrome respond to corticosteroid immunosuppression within 3 days. The duration of steroid therapy may range from 4 weeks to several months. For refractory cases of idiopathic tremor syndrome, diazepam (0.5 mg/kg PO q8h) or propanolol (2.5–10 mg/dog PO q8–12h) may be instituted. The rationale for propanolol treatment is based on the observation that catecholamines enhance physiological tremors in humans; therefore, beta-adrenergic antagonism of receptors in muscle and CNS may ameliorate tremors. Cyclosporine has also been reported anecdotally to be a useful adjunctive therapy for idiopathic tremor syndrome.

PROGNOSIS

Infectious meningoencephalomyelitis

The prognosis for infectious MEM (bacterial, CDV, protozoal, fungal) is dependent on the aetiology, duration, recrudescence of disease and severity of neurological signs. Rabies MEM is associated with a grave prognosis, as animals infected with rabies typically succumb to the disease within 3–10 days of initial neurological signs. The mortality rate for cats affected with CNS FIP is nearly 100%, with survival times ranging from weeks to months.

Idiopathic meningoencephalomyelitis

The prognosis for GME is considered to be poor without aggressive immunosuppression. The largest study of histopathologically confirmed GME cases included 42 dogs with survival times ranging from 1 to >1,215 days. The major factors affecting survival were neuroanatomical localization 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 died within a few days to weeks (median 8 days) of diagnosis. This large study suggests that GME has a poor prognosis, with most dogs succumbing to the disorder or being euthanized within a few weeks to months after diagnosis, despite steroid treatment. However, the study was limited to postmortem confirmed disease, so survival times and the associated prognosis may be biased towards dogs with severe GME.

A recent epidemiological study of Pugs with NME disclosed a median survival of 93 days (range, 1–680 days), with dogs receiving any form of treatment living significantly longer than those that were not treated. The prognosis for SRMA is fair to good, especially for dogs with acute disease that are treated with aggressive immunosuppression. Untreated dogs typically have a relapsing and remitting disease course. The prognosis for idiopathic tremor syndrome is generally favourable. Tremors typically abate in most dogs by the end of the first week of therapy. Some dogs relapse at the end of the treatment, requiring continued or adjunctive immunosuppressive therapy. Occasionally, relapses may occur after several months or years. Re-institution of prednisone therapy typically results in resolution of tremors within 5 days in relapsing cases.

Previous reports of combined prednisone and CA treatment protocols for MUA showed survival times of 46–1,025 days. In a more recent study comparing prednisone/vincristine/cyclophosphamide with prednisone/CA protocols for treatment of MUA, median survival times did not differ between the groups and were both >12 months. Side-effects with the cyclophosphamide

protocol were greater and more severe than with the CA protocol. Cyclosporine has also been evaluated for the treatment of MUA, with an overall median survival time (10 dogs) of 930 days (range, 60–1,290 days). Side-effects were minimal and included excessive shedding, gingival hyperplasia and hypertrichosis. The median survival time of 40 dogs with presumed MUA treated with prednisone and azathioprine was 1,834 days (range, 50–2,469 days). Finally, in a study of dogs with MUA comparing dogs treated with procarbazine and prednisone with dogs not receiving any treatment, median survival time was 14 months and 0.73 months, respectively.