

INFLAMMATORY BRAIN AND SPINAL CORD DISEASES: MORE COMMON THAN YOU THINK!

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DEFINITIONS

- Meningitis: inflammation of the meninges (the pia, arachnoid and dura mater; protective membranes covering the brain and spinal cord).
- Encephalitis: inflammation of the brain.
- Myelitis: inflammation of the spinal cord.
- Meningoencephalitis: inflammation of the meninges and brain.
- Meningomyelitis: inflammation of the meninges and spinal cord.

INTRODUCTION

Meningoencephalitis and meningomyelitis are common problems in small animal medicine. They may affect any breed of dog or cat, and animals of multiple ages, although certain disease processes are more common in specific breeds and age ranges (see below). Small and toy breed dogs in particular are frequently afflicted with inflammatory central nervous system (CNS) disorders.

CLINICAL SIGNS

A variety of clinical signs may be seen with inflammatory CNS disease, depending on what area of the nervous system is affected. Involvement of the forebrain (cerebral cortex and thalamus) may result in seizures, altered mentation (stupor, coma, delirium, head pressing), vision abnormalities, and compulsive pacing or circling. Involvement of the brainstem (pons and medulla oblongata) may result in altered mentation, cranial nerve deficits (e.g., vestibular dysfunction [head tilt, nystagmus], facial nerve paralysis, swallowing difficulties, tongue paralysis), ataxia, and proprioceptive deficits. Spinal cord involvement leads to ataxia, paresis, and possibly segmental spinal reflex deficits. Most inflammatory CNS conditions result in pain due to involvement of the meninges. A hallmark of these conditions is the presence of multifocal neurologic signs; that is, involvement of multiple areas of the CNS (e.g., forebrain, brainstem and spinal cord).

The majority of small animals with meningoencephalitis or meningomyelitis have signs restricted to the nervous system. However, involvement of other organ systems is possible with some infectious agents (e.g., systemic fungal or bacterial infections, rickettsial disease). Contrary to what many believe, fever is quite uncommon in most dogs and cats with meningoencephalitis.

DIAGNOSIS

The diagnosis of inflammatory CNS diseases in small animal patients involves consideration of the signalment, reported and observed clinical signs, and results of diagnostic testing. The most useful tests are advanced diagnostic imaging (particularly magnetic resonance imaging [MRI]), and cerebrospinal fluid (CSF) analysis. Although computed tomography (CT) is of some use in demonstrating brain lesions, MRI is the gold standard for brain imaging, and is much more sensitive in showing inflammatory lesions of the brain and spinal cord. Inflammatory lesions are typically hyperintense on T2-weighted, STIR, and FLAIR images, hypointense or isointense on T1-weighted images, and enhance to varying degrees after intravenous contrast administration (gadolinium compounds). Analysis of CSF in these patients typically shows elevated white blood cell numbers (pleocytosis) and protein. Cytology should be performed to determine the types of inflammatory cells present. Electrodiagnostic testing is less frequently used, but may provide useful functional information to complement the imaging and CSF results. Electroencephalography (EEG) and brainstem auditory evoked response (BAER) provide such information about the cerebral cortex and brainstem pathways respectively. Finally, testing for infectious disease agents may involve quantification of antibody titers or polymerase chain reaction (PCR)-based testing on blood and CSF samples.

TREATMENT

The therapy of meningoencephalitis and meningomyelitis should be tailored to the specific etiology or suspected syndrome, while taking into account the severity of the clinical signs, comorbid disease processes, and financial constraints of the owner. Patients with identified infectious etiologies should be treated with appropriate antimicrobial medications, which may include antibiotics, antifungals, or antiprotozoals. Whenever possible, medications with good penetration of the blood-brain barrier should be selected for therapy. Such choices often include doxycycline, sulfonamide drugs, and fluconazole.

Corticosteroids are a mainstay of therapy for inflammatory CNS conditions, regardless of etiology. Although immunosuppression and long-term treatment with corticosteroids is usually contraindicated for infectious processes, short-term therapy can dramatically reduce the inflammatory response, and can be life-saving. In addition, corticosteroids form the cornerstone of therapy for the inflammatory conditions without an underlying identifiable etiology. Although many animals benefit from anti-inflammatory doses of these medications, immunosuppressive doses are often required for disease remission. The doses of corticosteroids are generally reduced over an extended period of time to the lowest dose that controls clinical signs.

Many clinicians add additional immunomodulatory or cytotoxic medications to the therapeutic regimen of patients with meningoencephalitis of unknown etiology (MUE). Such drugs include cytosine arabinoside (cytarabine, Ara-C), cyclosporine A, leflunomide, mycophenolate mofetil, lomustine (CCNU), azathioprine, and procarbazine. These medications are useful to provide additional immunosuppression through

alternate mechanisms of action, and also to reduce the side effects associated with glucocorticoid therapy, which include polyuria, polydipsia, polyphagia, weight gain, panting, gastrointestinal ulceration, coagulopathies, pancreatitis, and steroid hepatopathy.

ETIOLOGIES AND SPECIFIC SYNDROMES

A variety of infectious agents may lead to nervous system dysfunction, including viruses, bacteria, fungal organisms, rickettsiae, protozoa, and parasites (see Table 1).

Despite the number of potential infectious etiologies, these are rarely identified as the underlying cause of meningoencephalitis or meningomyelitis in small animals. Although cats are often presumptively diagnosed with an infectious etiology, dogs are much more likely to fit into one of the syndromes described below that have no identifiable infectious cause.

Steroid responsive meningitis-arteritis

As its name implies, this is a condition that involves the blood vessels of the meninges, leading to vasculitis and meningitis. It typically affects young (6-18 months), large breed dogs, particularly Boxers, Bernese Mountain dogs, Weimaraners, and Nova Scotia Duck Tolling Retrievers.^{1,2} Beagles are also affected by this condition, which is also known as “Beagle Pain Syndrome”. Affected animals usually present for moderate to severe neck pain, with a low head carriage and reluctance to move. True neurologic deficits are uncommon with this disorder, although chronically affected animals may develop ataxia or paresis if left untreated,² and seizures have been rarely documented. Diagnostic imaging is often unremarkable but may show meningeal enhancement.² Cerebrospinal fluid evaluation typically shows a profound neutrophilic pleocytosis (cell counts often exceed 1000 cells/ μ l). Dogs presenting in the acute stages usually respond completely to immunosuppression with corticosteroids, and additional immunosuppressive medications are rarely required.^{1,3} However, more chronically affected animals may require additional immunosuppression and may have a more guarded prognosis.²

Generalized tremor (“little white shaker”) syndrome

This condition is commonly referred to as “little white shakers” or “shaker dog syndrome” due to its tendency to affect young toy breed dogs. However, it may affect dogs of any color or breed.⁴ Encephalitis mainly involving the cerebellum is thought to result in the predominant clinical signs. Dogs show an obvious, constant tremor, which may worsen with movement. Additional neurologic signs are not usually found, although other cranial nerve deficits (e.g., vestibular signs), paresis, and visual deficits have been described.⁵ This syndrome is often diagnosed based on clinical signs and response to therapy, and few descriptions of diagnostic imaging are available. Cerebrospinal fluid analysis usually shows a mild to moderate mononuclear pleocytosis, but may be normal.^{4,5} Affected animals typically respond completely to corticosteroids

and diazepam, which can usually be discontinued after a period of time.^{4,5} However, recurrence of signs is possible.

Granulomatous meningoencephalitis (GME)

This syndrome is named after the profound granulomatous inflammation of the brain of affected patients, characterized by perivascular infiltrates of macrophages, lymphocytes and neutrophils.^{6,7} The brainstem is usually the area most severely affected, and dogs typically present with signs of ataxia, paresis, cervical pain, and vestibular dysfunction. Other signs such as visual dysfunction, facial nerve deficits, dysphagia, pupillary abnormalities and seizures may also be seen.⁶ Clinical signs may vary from relatively mild to very severe with rapid decompensation and death. Certain breeds appear to be predisposed to the development of GME, including the toy poodle and terrier breeds. However, any breed of dog may be affected, and dogs of all ages may be seen.

Lesions noted on MRI are hyperintense on T2-weighted and FLAIR images and enhance to varying degrees after contrast administration.⁶ Lesions are often found in the brainstem, forebrain, and cervical spinal cord, while meningeal involvement is rarely noted on diagnostic imaging.⁸ Evaluation of CSF typically shows a moderate to severe mononuclear pleocytosis, although neutrophils can occasionally dominate the cytology.⁹ In rare cases the CSF is normal. The majority of patients will show improvement with corticosteroid therapy, although this improvement is often incomplete, and most animals require persistent long-term therapy. Relapses are frequent, particularly with attempts to reduce glucocorticoid doses. Many clinicians add additional immunosuppressive medications to improve control of clinical signs and reduce some of the side effects of the corticosteroids.^{6,10-14} Radiation therapy may be beneficial for some patients with focal inflammatory lesions.¹⁵ The long-term prognosis for these patients is guarded, as many relapse and eventually succumb to the disease.¹⁵ However, responses to treatment are quite variable, and in the author's opinion, this syndrome likely represents several different disease processes with varying etiologies and outcomes.

Necrotizing meningoencephalitis (NME)

This condition was first reported in pug dogs, and is still often known as pug encephalitis.¹⁶ However, other young, small and toy breed dogs are commonly affected with NME, including Maltese terriers, Chihuahuas, Shih Tzus, Boston terriers, Pekingese, Papillions, Pomeranians, and others.^{6,17,18} The forebrain is primarily involved with infiltration of lymphocytes, plasma cells, and macrophages at the gray-white matter junction. Chronically affected animals develop necrosis of brain tissue with cavitation.⁶ Seizures are a prominent clinical sign. Other signs include altered mentation, circling, visual dysfunction, proprioceptive deficits, cranial nerve deficits, and cervical pain. Brain imaging with MRI can show a variety of lesions including T2-weighted and FLAIR hyperintensities with variable contrast enhancement, loss of the distinction between gray and white matter, cavitated regions with CSF filling, and meningeal enhancement, predominantly in the forebrain.^{6,19,20} The lesions are usually asymmetric, with evidence of mass effect and occasional brain herniation seen. Cerebrospinal fluid evaluation

usually reveals a mild to moderate mononuclear pleocytosis, although cell counts are occasionally within normal limits.^{16,18} The response to therapy is less clear with this syndrome, although some dogs appear to respond to therapies similar to those utilized for GME (see above). These include immunosuppressive corticosteroids as well as other immunosuppressive or cytotoxic therapies.⁶ Prognosis is generally poor, although some dogs may survive for a year or longer before succumbing to the disease.

Necrotizing leukoencephalitis (NLE)

This syndrome is similar to NME, but predominantly affects the white matter of the forebrain and brainstem.⁶ This is primarily a disease of Yorkshire terriers, although other breeds have been reported, including the French bulldog.²¹ Affected dogs are typically young (6 months to 5 years of age). Clinical signs include seizures, altered mentation, visual deficits, circling, ataxia, and cranial nerve deficits. Magnetic resonance imaging usually reveals lesions within the white matter of the cerebrum and brainstem that are hyperintense on T2-weighted and FLAIR images, and hypointense on T1-weighted images with variable contrast enhancement.^{22,23} Computed tomography may show areas of decreased density within the forebrain and brainstem.²⁴ CSF shows a mild mononuclear pleocytosis or may be normal. Therapy is similar to NME, as is the prognosis.

Eosinophilic meningoencephalitis and meningomyelitis

Inflammatory CNS disease with a substantial eosinophilic component has been reported with several infectious etiologies including fungal and protozoal meningocephalomyelitis. However, an idiopathic syndrome resulting in similar clinicopathologic findings but without an identifiable infectious etiology has also been described.²⁵⁻²⁷ Young to middle-aged large breed dogs are predominantly affected and Golden retrievers and Rottweilers were overrepresented in some of these reports. Clinical signs may chiefly involve the brain, spinal cord or both regions. Peripheral eosinophilia was not found in the majority of cases described. Imaging of the CNS may show focal or multifocal lesions or may be normal.²⁷ Cerebrospinal shows a mild to marked pleocytosis with a substantial proportion of eosinophils (>20%). Most dogs respond dramatically and often completely to glucocorticoid therapy, which can often be discontinued after a period of time.^{26,27} The long-term prognosis for the idiopathic condition is good in most cases.

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Table 1. Infectious Agents Causing Meningoencephalomyelitis in Small Animals

Category of Agent	Specific Organisms
Viral	Canine distemper virus, FIP, FeLV, Rabies, Pseudorabies, West Nile virus
Fungal	<i>Cryptococcus neoformans</i> , <i>Coccidioides immitis</i> , <i>Blastomyces dermatidis</i> , <i>Aspergillus spp.</i> , <i>Cladosporium spp.</i>
Rickettsial	<i>Ehrlichia canis</i> , <i>Rickettsia rickettsia</i> , <i>Anaplasma phagocytophilum</i>
Bacterial	<i>Streptococcus spp.</i> , <i>Bartonella spp.</i> , <i>Borrelia burgdorferi.</i> , <i>Leptospira spp.</i>
Protozoal	<i>Neospora caninum</i> , <i>Toxoplasma gondii</i> , <i>Entamoeba histolytica</i>
Parasitic	<i>Cuterebra spp.</i> , <i>Dirofilaria immitis</i> , <i>Baylisascaris procyonis</i> , <i>Angiostrongylus spp.</i> , <i>Prototheca spp.</i>