Inflammatory CNS Diseases

Richard A. LeCouteur, DVM, BVSc, PhD, DACVIM (Neurology), DECVN
University of California
Davis, CA

Definition

Inflammatory central nervous system (CNS) diseases are a group of sporadic inflammatory diseases that affect the brain and/or spinal cord of dogs in the absence of an infectious cause (ie, pathogen-free).

Based on histopathological findings, 3 distinct forms of inflammatory CNS disease have been identified in dogs:

1. Granulomatous meningoencephalomyelitis (GME): Canine GME is the current term for an idiopathic CNS disease (most likely first described in 1936). GME still attracts a confusing and lengthy number of synonyms reflecting changes only in immunologic terminology (eg, inflammatory reticulosis, lympho-reticulosis, neoplastic reticulosis).
2. Necrotizing meningoencephalitis (NME): Canine NME was originally recognized in dogs in the U.S. in the 1970's as a breed-specific disease of pug dogs (colloquially known as "pug dog encephalitis"). Since 1989, based on morphologically defined lesion patterns and histology, NME has been recognized in other small-breed dogs, including Maltese, Chihuahua, Pekinese, Boston terrier, Shih Tzu, Coton de Tulear, and Papillon.
3. Necrotizing encephalitis (NE): Canine NE was first described in 1993 in Yorkshire terriers and has been reported in other breeds, including French bulldogs.

Signalment

- GME affects dogs older than 6 months of age, and is most prevalent in dogs between 4 and 8 years of age.
- Onset of NME is 6 months to 7 years of age, with a mean age of 29 months.
- NE typically manifests between 4 months and 10 years of age, with 4.5 years as a mean onset age.

Breed & gender predilection

- GME affects all sizes and breeds of dog (with toy and terrier breeds over-represented), whereas NME and NE affect predominantly small-breed dogs.
- Both males and females are affected, although females may be at higher risk of developing the disease.

Causes

- Obscure, although an autoimmune or immune-mediated/immune-dysregulatory cause is suspected.
- PCR-based screening for viral DNA (eg, herpes, adeno- or parvoviruses) has been negative.

Pathophysiology

- Suggested possible mechanisms include autoimmune encephalitis induced by anti-GFAP (glial fibrillary acidic protein) antibodies in CSF and T-cell-mediated delayed hypersensitivity mechanisms.

Clinical signs

- Signs of neurologic dysfunction reflect the location of the lesion(s) within the CNS.
- Multifocal involvement of the cerebrum, brainstem, cerebellum, and spinal cord (GME only) is common.
- Clinical signs of GME may include visual disturbances (ie, the ophthalmic form of GME affects the optic nerve), cranial nerve deficits (particularly central vestibular signs), seizures, apparent cervical pain, ataxia, and paresis.
- NME and NE frequently affect the forebrain, resulting in abnormal mentation, seizures, blindness, circling, and behavior changes, or brainstem, resulting in cranial nerve deficits, changes in mentation, and difficulty walking.

Diagnosis

A tentative antemortem diagnosis may be based on analysis of a combination of the patient's signalment, history, clinical signs, neurological examination findings, results of bloodwork, infectious disease titers, CSF analysis (including culture and PCR analysis), and advanced imaging (CT and MRI). Neurological signs, results of CSF analysis, and neuro-imaging findings will vary with intensity and location of the pathological lesions.

Definitive antemortem diagnosis is based on characteristic findings on histopathology of brain and/or spinal cord tissue obtained by surgical biopsy.

Definitive postmortem diagnosis is based on characteristic findings on histopathology of brain and spinal cord.

Differential diagnosis

Other causes of focal and multifocal CNS dysfunction of dogs (see Table 1).

Laboratory findings

CSF from dogs with inflammatory CNS disease usually is abnormal, although normal CSF may be present (particularly should corticosteroids have been administered up to 6 weeks prior to CSF collection).

Typical findings consist of an elevated total nucleated cell count and an elevated CSF protein. The predominant cell type is lymphocytes, with smaller numbers of neutrophils and macrophages present.

Infectious causes of the CSF abnormalities should be considered, and culture, serological testing, electrophoresis or PCR analysis (of CSF and/or serum) for the presence of infectious agents may be appropriate, although results of these tests are unlikely to contribute to a diagnosis.

Imaging

Characteristic findings on MRI include asymmetric, bilateral (often multifocal) lesions in the forebrain, brainstem, and/or spinal cord. These lesions variably enhance with intravenous contrast administration. Cystic areas may be seen in areas of the brain that are necrotic.

The classical lesions in GME, NME, and NE may be distinctly different based on both distribution pattern and microscopic lesions. While this information may be helpful in differentiating between the 3 forms of inflammatory CNS disease, it may not be possible to differentiate GME, NME, and NE based on imaging characteristics alone (except that spinal cord involvement is only present with GME).

Postmortem findings

A unique histopathological appearance is present in each of the inflammatory CNS disorders.

GME is characterized by a unique angiocentric granulomatous encephalitis consisting of a perivascular accumulation of macrophages often intermixed with lymphocytes and plasma cells. Three major patterns of histologic lesion distribution in brain and spinal cord have been described for GME: (1)The disseminated form, in which the most intense lesions occur in the upper cervical spinal cord, brainstem, and midbrain, often with less severe extension involving white matter of the rostral cerebrum. (2) A disseminated form with angiocentric expansion forming multiple coalescing mass lesions of similar distribution. (3) A focal form, in which single discrete mass lesions occur in either the spinal cord, brainstem, midbrain, thalamus, optic nerves, or cerebral hemispheres, without dissemination. It remains contentious whether this form is a neoplastic rather than an immunoproliferative process.

NME has both a characteristic anatomic distribution pattern and unique histological lesions. Gross lesions occur as asymmetrical, multifocal bilateral areas of either acute encephalitis or chronic foci of malacia, necrosis, and collapse of hemispheric gray and white matter decreasing in intensity rostrocaudally. Histologically, there is a unique combination of focal meningitis and polio- and leukoencephalitis of adjacent white matter. The lesions are intensely inflammatory with meningitis and parenchymal histiocytic, microglial infiltrates accompanied by perivascular cuffing of lymphocytes and plasma cells. Coexisting with chronic lesions can be acute nonsuppurative encephalitis in the hippocampus, septal nuclei, and thalamus. Usually, few inflammatory lesions are present in cerebellum, brainstem, and spinal cord.

In canine NE, grossly the large focal asymmetric bilateral malacic necrotizing lesions are confined mostly to the white matter of the cerebral hemispheres. There is an intense histiocytic, microglial and macrophage cellular infiltrate with loss of white matter and thick perivascular lymphocytic cuffing. Other areas have acute exudation, severe edema, necrosis, and eventual cyst formation, with a dramatic gemistocytic astrogliosis, histiocytes, and gitter cells intermixed with thick perivascular lymphocytic cuffing. Characteristically, the overlying cortex and meninges are not involved. Multifocal intense inflammatory cell infiltrates of macrophages with dramatically thick perivascular lymphocytic cuffing are seen in the midbrain, brainstem, and cerebellum.

Treatment

Therapy is based on the use of immunomodulatory drugs at immunosuppressive doses.

The most common therapy utilized is corticosteroids. Dogs often have a favorable response to corticosteroid monotherapy. Response to corticosteroids may be temporary.

Other immunomodulatory drugs may be used if the dog does not tolerate corticosteroids, to reduce the dose of corticosteroids, or if there is inadequate clinical response to corticosteroids. Many drugs have been recommended, including cyclosporine, procarbazine, lomustine (CCNU), leflunomide, mycophenolate mofetil (MMF), azathioprine, and cytosine arabinoside. All have been used by different authors in relatively small numbers of patients. There is no published evidence of the risks and benefits of these treatments when compared to the use of immunosuppressive regimens of corticosteroids alone for the same diseases. <Reviewer comment:

Regarding the use of drugs such as cytosine arabinoside, it seems that many feel that it may be very effective in acute encephalititis in improving clinical signs when corticosteroids alone are ineffective.>

The author recommends starting treatment with immunosuppressive doses of prednisone, giving the patient 1.5 mg/kg BID for 3 weeks; then 1.0 mg/kg BID for 6 weeks; then 0.5 mg/kg BID for 3 weeks; then 0.5 mg/kg once daily for 3 weeks. The patient then receives 0.5 mg/kg every other day indefinitely. After the first 4–6 weeks of prednisone therapy, cytosine arabinoside may be added at 3–6 week intervals (administered as a subcutaneous injection at a dose of 50 mg/m^2 Q 12 H for 2 consecutive days).

Precautions

Adverse effects of long-term high dose corticosteroid therapy include polyuria/polydipsia, polyphagia, weight gain, hepatotoxicity, gastrointestinal ulceration, pancreatitis, and iatrogenic hyperadrenocorticism.

Adverse effects of cytosine arabinoside are dose dependent, and include myelosuppression, vomiting, diarrhea, and hair loss.

Nutritional aspects

Avoid weight gain associated with prolonged corticosteroid administration.

Activity

Exercise restrictions are not recommended.

Client education

Clients should be informed that there is no definitive treatment for inflammatory CNS diseases of dogs. Therapy is aimed at suppressing the dog's immune system for as long as possible.

Prognosis is extremely guarded to poor.

Patient monitoring

Regular rechecks (suggested at monthly intervals or as needed) to assess progress of disease and to assess adverse effects of medications.

Repeat blood counts, chemistry panels, urinalysis, CSF analysis and advanced imaging procedures may be necessary.

Complications

Complications usually are related to adverse effects of immunomodulatory drugs.

Relative cost

Diagnosis and long-term management are costly due to need for specialized diagnostic procedures, immunomodulatory drug maintenance, and repeated assessments.

Prognosis

Prognosis for dogs with inflammatory CNS disease is poor, and most affected dogs eventually die from the disease, or are euthanized. Some survive only a short time, while others have a more prolonged clinical course, from 6 months to, rarely, years.

Future considerations

Research to date on canine inflammatory CNS diseases, and the nature of the histopathologic lesions, suggests the likelihood of an autoimmune or immune-mediated/immune-dysregulatory disease. In people, many autoimmune diseases have strong associations with certain MHC genotypes and this information may be used to assist in diagnosis or patient counseling. It is now possible to determine the MHC haplotype of dogs, and some disease associations with MHC haplotype in dogs already have been demonstrated. Assessment of MHC haplotype in dogs with GME may help to determine if there is a genetic component to disease susceptibility and development.

References

Clinical findings and treatment of non-infectious meningoencephalomyelitis in dogs: A systematic review of 457 published cases from 1962 to 2008. Granger N, Smith PM, Jeffery ND. *Vet J* 184(3):290-7, 2010.

Idiopathic granulomatous and necrotizing inflammatory disorders of the canine central nervous system: A review and future perspectives. Talarico LR, Schatzberg SJ. *J Small Anim Pract* 51(3):138-49, 2010.

Dog leukocyte antigen class II association in Chihuahuas with necritotizing meningoencephalitis. Vernau KM, Liu H, Higgins RJ, et al. *J Vet Intern Med* 24(3):736, 2010.

Table 1: Possible causes of brain dysfunction in dogs

Degenerative
☐ Lysosomal storage diseases
☐ Leukodystrophy/spongy degeneration
☐ Cognitive dysfunction syndrome
Anomalous/Developmental
☐ Congenital hydrocephalus
☐ Caudal occipital malformation
☐ Intracranial arachnoid cyst
Metabolic
☐ Hepatic encephalopathy
☐ Renal-associated encephalopathy
☐ Hypoglycemic encephalopathy
☐ Electrolyte-associated encephalopathy
☐ Endocrine-related encephalopathies
☐ Encephalopathy associated with acid-base disturbances
☐ Mitochondrial encephalopathy
Neoplastic
☐ Primary brain tumors
☐ Secondary brain tumors
Nutritional
☐ Thiamine deficiency
Inflammatory/Infectious/Immune-mediated
☐ Bacterial meningoencephalitis
☐ Fungal encephalitis
☐ Viral meningoencephalitis
☐ Protozoal meningoencephalitis
☐ Rickettsial meingoencephalitis
☐ Verminous meningoencephalitis
☐ Granulomatous meningoencephalomyelitis
☐ Necrotizing meningoencephalitis
☐ Necrotizing encephalitis
☐ Eosinophilic meningoencephalitis
Toxic
Vascular
☐ Ischemic encephalopathy
☐ Hemorrhagic encephalopathy