BRAIN FIRE – WHAT TO DO WITH CNS INFLAMATORY DISEASE

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Abstract: Inflammation of the CNS is a common neurological problem in dogs. In this session we will discuss the common causes, how we can investigate them and what treatment options exist.

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The hallmark of CNS inflammation is infiltration of peripheral blood leukocytes into the neuroparenchyma and its coverings, resulting in various types of encephalitis and/or meningitis, and sometimes associated with altered vascular integrity that leads to edema. The etiologies of inflammatory disease of the CNS are very diverse. Simplistically, they can be classed as pathogenic and non-pathogenic, with the latter being potentially related to immune-system dysfunction. Infectious causes may be viral, protozoal, bacterial, rickettsial, or fungal. The session will cover presentations and treatment approaches for each of the main causes. The notes below will just address the three top causes of CNS inflammation in the dog.

GRANULOMATOUS MENINGOENCEPHALOMYELITIS

Granulomatous meningoencephalomyelitis (GME) is a sporadic, idiopathic, inflammatory disease of the CNS of dogs. This disease appears to have a worldwide distribution, with recent reports coming from the USA, Australia, New Zealand, and Europe. The cause of GME is unknown.

Most cases of GME occur in small breed dogs, and commonly in terrier and toy breeds and Poodles, although any breed may be affected. The majority of confirmed cases occur in

young to middle-aged dogs, with a mean age around 5 years (ranging from 6 months to 12 years). GME occurs in both sexes; however, there appears to be a higher prevalence in females. A lack of obvious correlation between clinical signs and the course of the disease has been reported. Clinical signs usually reflect several (i.e. multifocal) syndromes, e.g., cerebral, brain stem, and spinal cord syndromes, as a result of the scattered distribution of lesions. However, focal signs have been reported in up to 50% of cases. Common signs include incoordination, ataxia and falling, cervical hyperesthesia, head tilt, nystagmus, facial and/or trigeminal nerve paralysis, circling, visual deficits, seizures, depression, and tetanic spasms. Occasionally, fever, peripheral neutrophilia, and excess non-segmented neutrophils will accompany the clinical neurological signs. An infrequently reported ocular form of GME appears to be related to lesions localized in optic nerves and optic chiasm resulting in visual impairment and abnormal pupillary reflexes.

A tentative diagnosis of GME may be suggested by signalment data, the clinical course of the disease, and clinical signs. Haematology, serum chemistry, and urinalysis studies are usually normal and electroencephalographic recordings are frequently non-specific. Rarely, an intrathecal filling-defect may be detected myelographically in dogs possibly due to focal cord swelling or subarachnoid granulomas. The most useful diagnostic aid is CSF analysis. In most dogs, CSF is abnormal with mild to pronounced pleocytosis, ranging from 50 to 900 WBCs/ul. Cells are predominantly mononuclear, including lymphocytes (60 - 90%), monocytes (10 - 20%), and variable numbers of large anaplastic mononuclear cells with abundant lacy cytoplasm. While neutrophils typically comprise from 1 - 20% of the cell type differential, they may be the predominant cell type on rare occasions. Occasionally, protein is elevated without pleocytosis. In one retrospective study of dogs with GME, lumbar-derived CSF contained fewer cells and less protein than CSF derived from cisternal puncture. CSF

protein and cellularity is not necessarily influenced by the degree of meningeal involvement or the extent of necrosis within the granulomatous lesions. A combination of CSF and MRI findings may also be useful, the latter being characterized by isointense lesions on T1-weighted images. Pial/dural meningeal enhancement may be found with MRI. Although infrequently performed, brain biopsy can be a very useful diagnostic test in animals with focal lesions.

Prognosis for permanent recovery is gaurded. Some dogs die from inhalation pneumonia secondary to megaesophagus. Shortest survival periods, ranging from several days to weeks, are seen with the disseminated and ocular forms. Longer survival periods of from 3 to 6 months, or longer, are more suggestive of a focal lesion. In one retrospective study of 42 dogs with GME , median survival time for dogs with focal versus disseminated disease was 114 and 14 days, respectively, and dogs with focal forebrain signs (e.g., seizures) had significantly longer survival times (>395 days) than did dogs with focal signs in other areas of the CNS (59 days). Long-term therapy is generally unsatisfactory, although temporary remission of signs is often achieved with corticosteroid administration, such as oral prednisone, 1 to 2 mg/kg/day initially for several days, then reducing the dosage to 2.5 - 5 mg on alternate days. Most dogs will require continued therapy to prevent recurrences of signs. Improvement may last for several days, weeks or months, although most will eventually succumb to the disease. Part of the temporary improvement may be related to a reduction of mast cell function in dogs receiving glucocorticoid medication. Cessation of glucocorticoid therapy is invariably associated with rapid and dramatic clinical deterioration. Results of a recent retrospective study suggested that radiation therapy (e.g., total doses ranging from 40 to 49.5 Gy, divided in 2.4- to 4.0-Gy fractions) may be an effective treatment for dogs with GME, particularly those with clinical signs suggesting focal involvement. Promising clinical

results following use of cytosine arabinoside (at 50 mg/m^2, SQ, bid x 2 days, repeat q 3 weeks) suggests that this potent anti-inflammatory drug may be an effective sole therapy for the long-term treatment of GME in dogs. Other immunosuppressive treatment options include mycophenolate, leflunomide, cyclosporine, cyclophosphamide and azathioprine.

NECROTIZING MENINGOENCEPHALITIS

Necrotizing meningoencephalitis is a chronic progressive neurological disorder reported in Pugs (Pug encephalitis), Yorkshire Terriers and Maltese dogs. There are also sporadic reports of similar findings in other small-breed dogs, such as the Chihuahua, Pekingese and Shih Tzu.

- Pug encephalitis is most commonly seen in juvenile to young adults, and causes seizures and other signs of forebrain dysfunction.
- The disease described in Maltese dogs also has a predilection for the forebrain
- The disease in Yorkshire Terriers causes signs of forebrain and brainstem involvement

Pathogenesis: The aetiology of the disease is unknown. Infection with an alpha-type herpesvirus has been suggested based on histological similarities with this type of infection in humans. However, attempts at viral isolation have been unsuccessful. The disease is associated with necrosis and a non-suppurative meningoencephalitis predominantly in the cortex. The subcortical white matter is frequently involved. Areas of necrosis can also be seen in the brainstem. Recent research suggests that genetics may play a role in disease susceptibility in Pugs

CT may reveal a focal hypodense area within the brain parenchyma relating to the area of necrosis. Multifocal, asymmetrical areas of high signal intensity in the brain can be seen on T2-weighted MR images, with variable contrast enhancement of the parenchyma and

meninges visible on T1-weighted images. A lymphocytic pleocytosis is most frequently recognized on CSF analysis. A definitive diagnosis is based on histopathology. Prognosis is poor and the disease is typically fatal. Combined immunosuppressive protocols similar to those utilized for the treatment of GME are recommended. As with GME, there is limited information on the efficacy of such treatments in cases of histologically confirmed disease.

BACTERIAL ENCEPHALITIS / MENINGITIS

Bacterial meningitis is a rarely reported condition in dogs and cats. Animals of any age may be affected, although most affected dogs are adult, with a mean age around 5 years. Bacterial infections of the CNS most often occur via haematogenous spread from distant foci within the body (e.g., lung or splenic abscess, vegetative endocarditis, pleuritis, and urinary tract infections), by direct extension from sinuses, ears and eyes, as a result of trauma (e.g., bite wound), meningeal spread with entry along nerve roots, or from contaminated surgical instruments (e.g., spinal needle). Organisms usually disseminate via CSF pathways and produce cerebrospinal meningitis, often associated with microabscess formation of brain and spinal cord. A plethora of organisms have been cultured from dogs with bacterial meningitis including *Pasteurella* sp (e.g., *P. multocida*), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus albus*, *Actinomyces* sp, *Nocardia* sp, *Escherichia coli*, *Streptococcus* sp (e.g., *S. pneumoniae*) and *Klebsiella* sp.

Irrespective of the etiologic agent, bacterial meningitis usually is acute in onset and tends to be characterized by a group of clinical signs that include hyperesthesia, fever, cervical pain, and frequently, cervical rigidity. In addition, vomiting, bradycardia, anorexia, occasional

cranial nerve deficits, and seizures may be observed. Seizures may be caused by high fever, hypoglycemia, brain edema, or inflammation, while vomiting may result from increased intracranial pressure or from direct effects on the vomiting center. In some animals, clinical signs may develop that suggest parenchymal involvement. The clinical diagnosis of bacterial meningitis is supported by the finding of highly pleocytic CSF (500 to 1000+ WBCs/ul) with a high proportion of neutrophil cells. The protein content of the CSF is usually increased as well (100 to 1000+ mg/dl). Low CSF glucose, relative to plasma glucose values, are typical. Organisms may be seen on CSF cytology. Neutrophilia may be present in blood samples and there may be evidence of shock, hypotension, and disseminated intravascular coagulation.

Prognosis is guarded since death is common even if appropriate therapy is administered, and relapses are frequently encountered. Appropriate use of antibiotics, according to the culture results, is basic to successful therapy of bacterial meningitis (encephalomyelitis). Antibiotic therapy should be maintained for several weeks after clinical signs have resolved.

PROTOZOAN ENCEPHALITIS-ENCEPHALOMYELITIS

Toxoplasmosis is an infectious condition caused by the protozoal parasite *Toxoplasma gondii* and occurs in acquired and congenital forms in man and animals. Cats are the definitive host for this parasite. TX-NS in dogs resulting in a systemic infection will typically affect most organs, and the CNS, in particular. Neurological signs associated with TX-NS encephalomyelitis are variable and may reflect a focal or multifocal disease process. In dogs, signs include hyperexcitability, depression, intention tremor, paresis, paralysis, head tilt, and seizures.

In the diagnosis of TX-NS neurological disease, abnormal hematological parameters may include non-regenerative anemia, neutrophilic leukocytosis, lymphocyosis, and eosinophilia. Serum alanine aminotransferase and aspartate aminotransferase levels may be increased, especially in dogs with acute hepatic and muscle necrosis. Results of CSF may be abnormal, with elevated protein content and a mixed monocytic-polymorphonuclear pleocytosis. An eosinophilic pleocytosis was found in 2 dogs with a granulomatous encephalomyelitis due to protozoan infection. Xanthochromia will be present if hemorrhage has occurred. Electromyographic testing may reveal fibrillation potentials, positive sharp waves, bizarre high-frequency potentials, and myotonic-like discharges. Nerve conduction velocities may be decreased. Serum creatine kinase levels are often increased. Protozoan meningoencephalitis has been detected using MRI scans. The close resemblance between *T. gondii* and *N. caninum* tachyzoites and tissue cysts prevents definitive diagnosis by histopathology, and the clinical syndromes appear to be identical. Differentiation between the two protozoan organisms can be made using assays for circulating antibodies, by tissue immunocytochemistry, and ultrastructural studies. Sensitive polymerase chain reaction assays have been reported for the detection of both *Neospora caninum* DNA and *Toxoplasma gondii* DNA in biological samples. Muscle biopsy of appropriate muscles (as suggested by the clinical signs) may also provide the possibility of a definitive premortem diagnosis using the aforementioned techniques.

Prognosis is poor when signs of pelvic limb spasticity are observed and is guarded in any animal with signs of CNS disease. In one study involving 27 cases of neosporosis, recovery was less likely in peracute cases with severe clinical signs, and when treatment was delayed. Many animals with myositis-polyradiculoneuritis have concomitant lesions in the CNS. A 4 to 8 week regimen of trimethoprim-sulfonamide (at 15 - 20 mg/kg combined dose, PO, bid)

and pyrimethamine (at 1 mg/kg, PO, daily) has successfully treated animals with TX-NS-induced encephalomyelitis and myositis-polyradiculoneuritis.

CANINE DISTEMPER VIRUS INFECTION

Canine distemper virus (CDV) is a paramyxovirus that commonly infects the CNS of dogs. The presence and severity of the neurological signs depend on factors such as the age and immunocompetence of the host and the neurovirulence of the virus strain. Many dogs probably develop transient CNS infections without concurrent clinical signs. In the CNS, CDV initially replicates in the neurons and glial cells, and can cause both grey and white matter lesions, with one usually predominating. These early degenerative lesions are not characteristically inflammatory. A chronic course of CNS infection results from a late or insufficient immune response to CDV, with characteristic inflammatory demyelinating lesions. Polioencephalomyelopathy (PEM) has been reported most frequently in immature dogs, whilst leucoencephalomyelopathy (LEM) or a combination of PEM and LEM is more common in mature animals.

An indirect fluorescent antibody test for viral antigen in conjunctival smears can be positive in many dogs with CNS distemper, regardless of whether the disease is acute or chronic. Viral antigen can also be demonstrated in tracheal washings and urine sediment.

Results of CSF analysis are variable. During the acute stage of the disease, an inflammatory response is lacking and thus the cell count and protein levels can be normal. In the chronic stage of the disease, lymphocytic pleocytosis is more frequently identified. An elevated CSF titre of antibody against CDV relative to the serum titre is supportive of a diagnosis.

There is no specific treatment for CDV-associated neurological disease. Overall, prognosis is poor, especially in cases with rapidly progressive signs. Seizures are reported to be an

unfavourable prognostic sign as they are often difficult to control with antiepileptic drugs. However, the disease is not fatal in all instances and some animals recover. Consequently, in cases where the neurological signs are not severe, it is recommended that the animal is provided with supportive care and the disease progression monitored over 1--2 weeks before considering euthanasia.