Inflammatory diseases of the CNS have been reported to be very common causes for neurologic
disease in dogs. These diseases are divided into infectious and non-infectious categories. Of the
non-infectious diseases, the main diseases include granulomatous meningoencephalitis (GME),
eosinophilic meningoencephalitis, sterile responsive tremor (Idiopathic White Shaker
Syndrome) and breed specific encephalidities (necrotizing meningoencephalitis). Recently,
some have suggested the use of the term meningoencephalitis of unknown origin (MUO) in
dogs that have definitive evidence of CNS inflammatory disease (abnormal imaging or CSF) and
for which no histopathology is available for a definitive histopathological diagnosis. While these
diseases all seem to have immunological and genetic components, they each have distinct
pathological features and variable prognoses. Steroid responsive meningitis-arteritis is also a
non-infectious inflammatory disease, however, this tends to be a systemic disease.

**Granulomatous Meningoencephalitis**

Granulomatous meningoencephalitis is a term used to describe a condition that is probably an
immune mediated disease of the central nervous system (CNS) of dogs. Granulomatous
Meningoencephalitis is an inflammatory disease of the central nervous system. It consists of
predominately mononuclear cells. At present no infectious cause has been found and there is
no evidence of neoplastic disease process.

**Etiology and Pathology:** GME is an important disease with a reported incidence of 5-25% of
all CNS disease in dogs. The cause for GME is unknown. Various etiologies have been
investigated including viral infection, neoplasia, and immune mediated disease. At this time,
most consider this to be an autoimmune inflammatory disease. Research suggests it may be a T
cell-mediated delayed-type hypersensitivity based on a predominance of CD3+ T-lymphocytes
on histologic analysis. Macrophages also contribute to the pathology of the disease. GME is
characterized by a proliferation of mononuclear cells around CNS vasculature. There are three
forms of the disease described: Disseminated, Focal, and Ocular. GME may affect any portion of
CNS, but is more commonly found in the brain. Perivascular accumulations of mononuclear cells
may form variable sized granulomas. These angiocentric lesions consist of whorled
accumulations of lymphocytes, large mononuclear cells, plasma cells and fewer neutrophils.
Within the brain parenchyma the pathology is present mainly in white matter.

**Signalment:** GME is most common in small or toy breed dogs such as Toy Poodles, Miniature
Pinschers, Yorkshire Terriers, and Chihuahuas. In general, affected dogs tend to be young to
middle aged. A range of six months to 12 years, with a mean age of 5 years has been reported.
Females may be affected more commonly, with a ratio of 1.8:1 up to 3:1. Any dog, of any age can develop GME.

**Clinical Signs:** The clinical signs of GME are extremely variable and are most dependent on the location of the lesion. Neurologic signs may be acute or chronic. About 50% of focal signs are related to forebrain disease (seizures, behavior changes). About 50% of dogs have forebrain and brainstem involvement. Central vestibular signs (head tilt, falling) are common with GME. Neck pain may also be a feature of the disease, possibly due to meningeal involvement. Some reports state that dogs may have fever or leukocytosis with this disease, although the author does not find this to be common and in these cases is much more likely to search for an infectious disease.

**Diagnosis:** The diagnosis of GME is made in most cases using a combination of imaging and cerebrospinal fluid (CSF) analysis. Advanced imaging (MRI, CT) has helped with the identification of this disease and to. MRI is considered to be the most sensitive form of imaging, although CT allows granulomas to be identified in many cases. Contrast should be used with either form of imaging.

Important negative prognostic factors for survival on MRI include foramen magnum herniation, loss of cerebral sulci, and mass effect. CSF collection and analysis is usually done following imaging. The classic pattern of GME found in CSF is a mononuclear pleocytosis (increased white count) with lymphocytes, activated macrophages, and an increased protein concentration. In some dogs, the CSF may contain a small proportion of neutrophils. CSF is not always reliable since in some dogs there are no abnormalities present. A biopsy is required for a definitive diagnosis, although this is rarely done. In the past, infectious disease titers (Toxoplasma, Neospora, Tick Borne Disease, Cryptococcus) were recommended, however several studies have failed to show a connection with infectious disease. This testing is generally negative and increases diagnostic costs. The definitive diagnosis of GME antemortem can be difficult.

**Treatment:** The treatment of GME is immunosuppression. The use of corticosteroids is the cornerstone of this type of therapy. Corticosteroids affect humoral and cell-mediated immunity and act quickly to control disease. For effective immunosuppression: -Prednisone 2-4 mg/kg/day or 2.2 to 6.6 mg/kg/day in divided doses or -Dexamethasone 0.6 to 2.2 mg/kg divided.

The induction of immunosuppression may take 10-28 days, although a clinical response is seen much sooner. Corticosteroids have many well documented side effects, and they are not always effective in controlling GME. Recently other immunosuppressive agents have been used to significantly improve the response to treatment for many dogs. A 2010 meta-analysis of immunosuppressive regimens for this disease which evaluated 71 studies and a total of 457 dogs were unable to demonstrate an optimal immunosuppressive protocol. A partial list of drugs used includes Cytosine arabinoside, Cyclosporine A, Lomustine, Azathioprine, Procarbazine, Myocophenolate Mofetil, and Leuflonamide. Radiation has also been reported to be effective for focal disease. Currently, a popular treatment is the use of corticosteroids with
Cytosine arabinoside (Cytarabine). While large scale studies are lacking, anecdotal evidence suggests this can be an effective treatment. Also the use of Cytarabine is associated with minimal side effects. Cytosine arabinoside is a pyrimidine nucleoside antimetabolite with the primary adverse effect of myelosuppression. This drug crosses the blood brain barrier where it undergoes enzymatic activation. It then competes for incorporation into nucleic acids and competitively inhibits DNA polymerase in mitotically active cells. This drug also interferes with topoisomerase and prevents DNA repair. Cytarabine is given at a dose of 50-100 mg/m² subcutaneously every 12 hours for a total of 4 doses. This is repeated every 3-4 weeks. In severely affected dogs the author uses an IV infusion of 200 mg/m² over 48 hours. The drug is eliminated in the urine. A CBC should be evaluated periodically during treatment.

In more mildly affected dogs, the author has had success using prednisone in combination with azathioprine, a purine antagonist immunosuppressive agent. This drug is given orally and is generally well tolerated. The principal adverse effect is bone marrow suppression and the drug can cause potential GI and liver disease.

Cyclosporine A (Atopica) is an immunosuppressant that targets cell-mediated immune responses. It has also been shown to be effective in some dogs with GME. This drug may cause vomiting, anorexia, and diarrhea. The main problem with this drug is cost.

Radiation has also been described as a form of immunosuppression used to treat this condition. Dogs with focal and multifocal forms of the disease were treated. Recently a 30 Gy 10 fraction protocol given over two weeks was described in six dogs concurrently receiving corticosteroids. A median survival time of 476 days was reported.

**Prognosis:** The prognosis for GME is variable. Older literature states that the presence of multifocal disease or involvement of the brainstem are negative prognostic factors, however, this does not always seem to be the case. Many dogs respond to corticosteroids and Cytarabine. Dogs may live for years with this condition. Some dogs do not respond to treatment and it can be difficult to predict which dogs will fail treatment. Clients should be counseled that this is a long-term treatment and that stopping therapy may result in relapse. The long-term use of steroids has many potential negative aspects. Furthermore long-term treatment can be financially difficult for some owners. Prognosis for this condition is difficult to ascertain since most studies that histologically document GME are post mortem studies and therefore biased. There is a recent report that did not use histopathology but rather MRI and CSF analysis for the diagnosis of MUE. It also did not discern NME from GME. In this report 56% of dogs with MUE died or were euthanized within 3 months. The median survival of these dogs was 2 days. However, if dogs lived longer than 3 months their prognosis was good to excellent. This subset of patients had a median survival of 1616 days. All of these dogs were treated with a combination of prednisone and cytarabine. Relapse was common in these dogs when treatment was discontinued.
**Necrotizing Encephalitis**

Idiopathic Necrotizing Encephalitis is a disease that in some ways is similar to GME. The main difference clinically is that this disease, despite treatment, is generally fatal. The cause for NME is unknown, but it is most likely an immune mediated disease. The cause probably has a genetic as well as environmental component. Recently a novel genetic risk loci was identified in Maltese Dogs with NME. This study also showed a shared genetic risk among toy breed dogs associated with Chromosome 15 and the dog leukocyte antigen (DLA) class II complex. NME has been reported to be breed specific and occurs in juvenile to young adults. In the Pug and Maltese breeds, it is a nonsuppurative meningoencephalitis. The lesions are present in the cerebral hemispheres. Clinical signs of NME include seizures, depression, circling, behavior changes, and reduced vision. Some affected animals die quickly. The histological lesions consist of severe necrotizing meningoencephalitis in the cortical leptomeninges. There is also paraventricular inflammation involving both gray and white matter. Tissue necrosis may be extensive and inflammation may be more severe in white matter (NME). Some dogs may have cavitation of brain tissue. Histological samples show perivascular and parenchymal infiltrates of lymphocytes, plasma cells and histocytes. A similar condition that occurs in the Yorkshire Terrier and Chihuahua is Necrotizing Leukoencephalitis (NLE). This predominately involves the white matter of the forebrain and brainstem. A recent study reported NME in other breeds: a Papillon, Shih Tzu, Coton de Tulear, and Brussels Griffon. There is another report of NME occurring in a 4 year old 26 kg Staffordshire Bull Terrier Mix indicating larger dogs may be affected by this disease. This indicates that Necrotizing encephalitis is not a breed restricted disease and is a possible consideration in dogs with changes on MRI and CSF supportive of the disease. Diagnosis of these conditions is similar to GME: imaging, CSF analysis, and in some cases biopsy. MRI and CT images may appear to be more severe than is many cases of GME.

There is no effective treatment for this condition. The period between onset of clinical signs and death can be rapid (weeks to months). Aggressive immunosuppression (corticosteroids and Cytarabine) may improve the survival times in some dogs based on anecdotal reports.
Steroid Responsive Meningitis/Arteritis (necrotizing vasculitis, polyarteritis, aseptic suppurative meningitis, Beagle Pain Syndrome) is an immune mediated disease that results in severe neck pain in affected dogs. It can occur in any dog but certain breeds have a higher incidence. Signs may develop from 3 months to 9 years, however generally affected dogs are 6-18 months of age. The most commonly affected dogs include Boxers, Beagles, and Bernese Mountain Dogs. These dogs tend to be juvenile or young adults. The cause of the condition is unknown but recent evidence shows there is a T helper 2-cell (Th-2) mediated immune response. An abnormal production of IgA is noted in the CSF and serum. The activated T cells are consistent with stimulus by an antigen as is reported for dogs with IMHA, however recent studies have failed to show a trigger such as an infectious disease, recent vaccinations, drug administration or neoplasia. Pathologic changes are found in the leptomeninges and arteries. Other organs affected include vessels of the heart, mediastinum, thyroid gland and joints. There are two forms of this disease, a “classic” acute form and a more chronic form. Clinical signs tend to be waxing and waning and include episodic fever, severe cervical pain, depression, loss of appetite and in later stages paresis. Initially a CBC will demonstrate a mature neutrophilia. Spinal fluid tends to have increased protein concentration and large numbers of neutrophils in addition to elevated IgA concentrations. Elevated CSF and serum IgA help identify SRMA over other inflammatory diseases. The cause for the elevation in IgA is likely the result of up regulation of the humoral immune response. In more protracted cases the cells become mononuclear. There is not a definitive anetemortem test for SRMA. The diagnosis takes into account the clinical signs, laboratory changes and ruling out other diseases. Acute phase proteins, which include C-reactive protein (CRP) and alpha2 macroglobulin are elevated in the serum of dogs with SRMA. However, other diseases can cause this response. After confirming SRMA, serum CRP concentrations can be monitored to evaluate the efficacy of treatment which makes it unnecessary to perform repeated CSF collection. CSF IgA concentrations do not decrease with successful treatment and are therefore not used for monitoring. Other inflammatory diseases should be ruled out, however most infectious disease testing is negative and the usefulness/cost effectiveness of this testing has been questioned. In a recent study of the risk for developing SRMA, the only significant factor was breed. The risk of developing SRMA is significantly increased for Boxer, Beagles, Weimaraners, and certain other breeds. No association could be made with the time of year, recent vaccination, or the sex of the dog or castration.

Recommended treatment consists of immunosuppression using prednisone, and in many cases combination therapy with Azathioprine. Treatment will be required for 4-6 months and in some instances much longer. Recurrence of signs can be due to too short a duration or dose of steroids.

1) Prednisone: 2 mg/kg PO q12h for 2 days; then taper to 1 mg/kg PO q12h for 2 weeks and then 1 mg/kg PO once daily for 2-4 weeks: Then taper very slowly over 6 months, depending on clinical signs and results of csf analysis.
2) Azathioprine: 1.75 mg/kg – 2 mg/kg PO q24 hours for 14 days then q48h until
resolved. The author tends to add this early in the course of treatment since side effects of prednisone tend to be severe over time.

Little has been written lately about use of additional immunosuppressive agents for treatment of this disease. However, mycophenolate mofetil (MMF) has been developed as an alternative to azathioprine. This drug has multiple properties affecting Lymphocyte production as well as inflammation. While limited information is available regarding the use of this drug in dogs, the side effects tend to be mild and consist of diarrhea and weight loss.
Suggested Reading:


Steroid Responsive Tremor

This syndrome is also called “Little White Shaker Syndrome”, idiopathic tremors, or cerebellitis. The cause of the tremors is unknown but is likely an immune mediated inflammatory brain disease that affects the cerebellum. Originally described in small white dogs (Maltese, West Highland white terriers), steroid responsive tremors can occur in dogs of any color or breed (miniature pinscher or toy poodle). Differentials include a toxicity (moldy dairy products – mycotoxins, metaldehyde, organophosphates), hypoadrenocorticism, and hypocalcemia.

This is a tremor syndrome that can be quite severe and incapacitating. Dogs with this condition generally have a sudden onset of constant whole body tremors. Tremors may be mild and affect only some regions of the body, such as the head, trunk, or limbs. Tremors may be so severe that the animal cannot walk and may not eat or drink. The animal with this condition has normal mentation. Shaking generally gets worse with activity/movement and then subsides with rest/sleep. Some dogs show overt signs of cerebellar disease (intention tremor, head tilt, loss of menace, nystagmus). Severe tremors may cause an increased body temperature. The diagnosis of this condition is based on a thorough history (toxin exposure) and hematological evaluation (CBC, serum chemistry), possibly followed by advance imaging (MRI is ideal to evaluate the cerebellum). Cerebrospinal fluid may be normal or show a mild mononuclear pleocytosis.

Treatment of this condition involves immunosuppression using Prednisone 1-2 mg/kg PO q 12 hours for the first few weeks with a gradual reduction in dose over 2-4 months. This may not be an adequate length of time for treatment, and therefore signs may recur. If this happens, prednisone therapy is resumed at the original dose, and I generally add azathioprine. Diazepam may be used in the early stages of the disease to reduce tremor severity. This drug may be given orally (0.5 mg/kg PO TID) or as a constant rate infusion (0.25-0.5 mg/kg/hr).

Suggested Reading:
