Treatment of Autoimmune Diseases of the Central Nervous System of Dogs

By Allen Sisson, DVM, MS, DACVIM (Neurology)
angell.org/neurology
neurology@angell.org

Several inflammatory, primary central nervous system (CNS) derangements of dogs have been described such as:

1. Granulomatous Meningoencephalomyelitis (GME)
2. Necrotizing Encephalitis of mostly Pug, Maltese and Yorkshire terrier dogs
3. Corticosteroid-Responsive or Neutrophilic Meningitis
4. Eosinophilic Meningoencephalomyelitis

5. Idiopathic Tremor Syndrome or Cerebellitis
6. Pyogranulomatous Meningoencephalitis

These conditions are considered to be idiopathic, since no causative agent or infectious organism has been found, and they respond to immune suppressive therapy. Because of this, it is now believed that these diseases are immune mediated (autoimmune) disorders. In most, but not all, cases with aggressive immunosuppressive therapy permanent remission can be achieved.

Depending on where in the brain and spinal cord these diseases start, and how rapidly they progress, they can cause a wide variety of signs. The most common presenting clinical signs are:

1. Progressively worsening central vestibular signs
2. Progressively worsening seizures and behavior abnormalities
3. Progressively worsening neck and or back pain
4. Progressively worsening para or tetraparesis
5. Progressively worsening generalized severe intention tremor
6. Acute onset of blindness

These signs can progress at various rates, but surprisingly they are often acute (1-2 days) to peracute (8-12 hours) in duration on initial presentation. In the peracute form these autoimmune brain and spinal cord diseases can be one of the most serious neurological emergencies. It is possible for a dog with GME involving the brain stem to progress from mild vestibular ataxia to severe violent rolling to opisthotonos, coma and death within 12-24 hours from the first onset of clinical signs. A dog with GME involving the cervical spinal cord may progress from signs of mild ataxia to full tetraplegia in 1-2 days mimicking a cervical disc herniation. Pugs, Maltese terriers and Yorkshire terriers with necrotizing encephalitis commonly present with only 1-2 days or even a few hours of pacing, demented behavior followed by near constant seizure activity and death within 12 to 24 hours.

Although in most cases a neurological patient should be stabilized and diagnostic tests evaluated before treatment is started, a dog with rapidly progressive GME or necrotizing encephalitis may be dead, or permanently neurologically damaged, if treatment is withheld for 8-12 hours so a cerebrospinal fluid (CSF) analysis and advanced imaging can be evaluated

before treatment is begun. It is therefore imperative that a high index of suspicion be maintained for autoimmune CNS disease when dogs are presented with unusually rapidly developing seizures, vestibular signs, tetraparesis, violent generalized tremors or blindness. Frequent, accurate neurological examinations will indicate if rapidly progressive or static to improving disease is present. For this reason do not admit a dog that appears to have acute onset geriatric vestibular disease with plans to re-evaluate the dog the next morning. If the dog has GME death may occur by then. If rapid neurologic deterioration is noted on repeat examination then immediate referral to a 24-hour emergency center or aggressive immunosuppressive therapy should be started until a CSF analysis and advanced CNS imaging can be done to confirm the diagnosis. Increased cellularity of a CSF analysis is not likely to be altered by corticosteroid or other immunosuppressive therapy for 12 to perhaps 24 hours; so an accurate diagnosis can still be made after glucocorticoid therapy has begun. However, if CSF is collected after 12-24 hours of glucocorticoid therapy false negative results are often obtained. Therefore you must begin, or refer the dog for, diagnostic testing as soon as possible after initiating therapy in such an emergency situation.

High dose, long term, immunosuppression is the key to successful therapy for all autoimmune diseases of the CNS. For this reason it is imperative that infectious causes of CNS inflammation be ruled out by diagnostic testing since immunosuppressive therapy would obviously worsen these conditions. The following therapies have been found to have efficacy in treating CNS autoimmune disease:

1. Corticosteriods in immunosuppressive doses
2. CCNU
3. Cyclosporine Modified by Microemulsion-Atopica
4. Cytarabine
5. Leflunomide
6. Procarbazine
7. Radiation Therapy

Corticosteroids, primarily prednisone, is the drug of first choice and is often used as the sole therapy. It is important that immunosuppressive doses be used initially, and therapy be sustained at high doses, very gradually tapered

over many months or relapses are likely to occur. A six-month tapering dosage schedule of prednisone that often works is as follows:

- 1 mg/lb Q 12 hours for 4 days
- 0.5 mg/lb Q 12 hours for 17 days
- 0.5 mg/lb Q 24 hours for 35 days
- 0.25 mg/lb Q 24 hours for 60 days
- 0.25 mg/lb Q 48 hours for 60 days

Dogs weighing less than 5 kgs are dosed as 5 kg dogs, and dogs weighing 5 to 10 kgs are dosed as 10 kg dogs. Dogs weighing over 35 kg are dosed as 35 kg dogs. Prednisone alone, used in the above dosage schedule, in about 75 percent of cases will cause permanent remission when neutrophilic or eosinophilic meningitis or focal GME of the posterior or rostral fossa of the brain are treated.

Prednisone alone or in combination therapy causes many adverse effects. When these adverse effects are severe they may require the prednisone dose to be reduced prematurely or even stopped entirely and another immune suppressive drug used in its place or combined with a reduced prednisone dose.

Some of the more common adverse effects can be prevented by some simple instructions to the owner. If the dog has normal renal function, the owner should limit the dog's water consumption to 20 ccs/pound of body weight divided three times a day. This will prevent the excess drinking that causes the dog to urinate in the house and be urinary incontinent. If the dog does start urinating in the house despite this, the dog's urine should be cultured using a cystocentesis urine sample to be sure a urinary tract infection has not developed. The dog should not be fed more than the amount of food he was fed before prednisone therapy. That should be 20 calories of food per pound per day. Feeding a high fiber, low fat food, such as canine or feline RD or feline WD, prevents weight gain and prevents the steroid induced colitis diarrhea that is very common unless this diet is used. The dog should have a 12 hour fasted serum chemistry profile collected in all cases 10 to 14 days after this prednisone schedule is started. If the serum bilirubin is elevated above the normal range the prednisone dose should be immediately reduced to 0.5

mg/lb once a day and the steroid hepatopathy should gradually start to resolve.

Alternative therapies: If these conditions relapse when prednisone therapy is reduced or discontinued, then other chemotherapeutic agents such as lomustine or cytarabine (used for 1 year) and/or microemulsion cyclosporine (used for 1.5 years) can be added to achieve permanent remission. Dogs with GME involving the spinal cord or visual pathways or that have necrotizing encephalitis should be treated with combination therapy of prednisone, lomustine, cytarabine and cyclosporine modified from the outset if they are to survive long-term. Leflunomide therapy can also be used to treat resistant cases that relapse despite combination therapy with other drugs.

*For more information, please e-mail neurology@angell.org or call **617 541 5140** to arrange a referral. More information is also available at www.angell.org/neurology.*