

Common and Deadly: Inflammatory Disease of the Brain and Spinal Cord William Bush, VMD, DACVIM (Neurology)

Introduction

When there are inflammatory cells within the brain, spinal cord or meninges then the terms encephalitis, myelitis, and meningitis are used, respectively. When inflammation is in more than one area the terms are combined like with meningoencephalomyelitis. The inflammation in these cases is most often from a non-infectious, unknown etiology and therefore called meningoencephalomyelitis of unknown etiology (MUE). The signs of the disease are specific to the location of the inflammation and most cases respond well to aggressive immune suppression. This talk discusses the terminology, definition / histopathology, common presentations, treatment and prognosis for different manifestations of non-infectious inflammatory disease within the nervous system

Terminology

MUE is an umbrella term for necrotizing encephalitis (NE) and granulomatous meningoencephalomyelitis (GME). Necrotizing encephalitis implies death of neurons within the brain from inflammation and is further subdivided into Pug dog encephalitis or necrotizing meningoencephalitis (NME) and Yorkshire terrier encephalitis or necrotizing leukoencephalitis (NLE). MUE has replaced these terms since multiple breeds have been identified with these disease and the prognosis, testing and treatment protocols are similar. Steroid responsive meningitis-arteritis (SRMA) is another non-infectious inflammatory disease that typically involves only the meninges – this disease will be discussed separately at end of this talk.

Definitions and Signalments

NLE was first described in the Yorkshire terrier. NLE is a progressive disease with an acute or chronic onset where there is necrosis of the white matter that with time, can coalesce into cavities or holes in the brain. The grey matter and spinal cord are spared in this disease. The other form of NE, NME first described in the Pug dog has since been noted in many other small breeds like the Maltese, Brussels Griffon, Colon du Tulear, Shih Tzu, and Papillion. NME is typically an acute onset and rapidly progressive disease of the both the grey and white matter of the cerebrum, with only 25 % of cases showing any multifocal or brainstem signs. Because the cerebrum is so commonly affected, seizure is common clinical sign - 94% of Pugs with this disease have seizure. GME is common and may account for up to 25% of canine CNS disease – it is an acute onset, progressive and potentially fatal disease. Unlike NE, the disease can manifest in the cerebrum, brainstem and spinal cord – 8 % of all cases present with only spinal cord signs. Histopathologically GME is noted most often in the white matter as perivascular infiltrates of round cells (plasma cells, lymphocytes and occasionally lymphoblasts) - these can coalesce to form tumors (unlike NE where the lesions coalesce to form cavities within the brain) (SJSR). Female, small breed dogs like the Miniature poodle, Maltese, Dachshund, Westie, and Chihuahua are commonly affected. Most dogs with GME are 4-8 years of age, whereas with NE most dogs are under 4 years of age. The take home point is that **MUE should be suspected in small breed under 8 years of age** with acute onset of brain and less commonly spinal cord signs.

Signs of Disease with MUE

The signs of disease are specific to the region of the brain that is involved. Most cases of MUE presents with multifocal clinical representing a mixture of forebrain and brainstem signs which can include altered mentation, visual deficits, central vestibular signs, proprioceptive placing and hopping deficits and seizures. In one report, 8% of cases has only spinal cord signs (weakness, paralysis, ataxia).

What is the cause of MUE?

The causes of MUE is thought to be from a genetic predisposition coupled with environmental exposures leading to a pathologic immune response. For instance, the histopathological differences in NE may result from minor differences among breeds, modifying genes, or variations in antigenic exposure. Breed predispositions indicate there is a heritable component to development of MUE. In the Pug, heritability

has been proven and a strong association demonstrated between affected dogs with single nucleotide polymorphism within the dog's leucocyte antigen (DLA) complex II region located on chromosome 12. The authors point out that this same association is made in human multiple sclerosis (MS) patients and that NME in the Pug dog maybe a good model for the less common acute variant forms of MS. Recent work in Maltese with NME show risk loci on chromosome 4 and 15.

MUE has been associated with viral diseases like Borna virus, West Nile, Canine parainfluenza, and Encephalomyocarditis virus, Canine herpes virus-1, Parvovirus, Porcine herpes virus-1, Bunya- and Polyomaviruses. Additionally, DNA from *E. Coli*, *Mycoplasma canis*. and *Bartonella vinsonii subsp berkhoffii* have been identified in sporadic cases of MUE and a recent report shows DNA from *Anaplama phagocytophilum* in 4/23 cases SRMA. These pathogens are not thought to be direct cause of the disease but according to the "Hit-and-Run Hypothesis" work in tandem with genetic and other environmental factors (vaccination?) to generate an autoimmune response, perhaps through molecular mimicry.

Autoimmune disease is likely in MUE because the CSF and serum of dogs with MUE contain an anti-astrocyte autoantibodies against glial fibrillary acidic protein (GFAP) which is an intermediate filament protein important in astrocyte function. Recent work has shown that the active cellular proliferation is thought to occur within the CNS lesion (and not from a migration from outside the CNS) and is assisted by matrix metalloproteinases (MMPs). MMPs are enzymes necessary for migration of leukocytes into the CNS or CSF and MMP-9 is elevated in some dogs with MUE. Other work by Dr. Mariani has also shown elevations in many interleukins necessary for lymphocyte proliferation and trafficking into tissue. However, to date there is no useful serum or CSF biomarker to assist in the diagnosis or treatment of MUE.

Lastly, since some cases of MUE lesions contain small amount of lymphoblasts and some are truly shown to be lymphoma at the time of histopathology, it is theorized that MUE is a lymphoproliferative disorder with features of both inflammation and neoplasia. Further support for this claim is the marked clinical responses of certain cases to chemotherapy.

MUE Diagnosis

An MUE diagnosis is based on clinical suspicion from the signalment and disease progression, and then MRI, CSF and infectious disease testing. It can be difficult ruling-out infection because of inaccurate test results and the fact that there are not tests for all known pathogens. For example, we had a suspected MUE whose necropsy revealed a high burden of an unknown protozoal agent. Complicating things further is not all cases will have an abnormal MRI and between 12-25% of MUE cases will have normal CSF analysis. In cervical spinal cord MUE, MRI of the paraspinal cervical muscles with STIR sequence in MUE is often abnormal (78% sensitivity) and rarely abnormal in normal controls (92% specificity) – because CSF results can be normal in cases of spinal cord MUE about 10% of the time, this sequence is important in suspected cases of cervical and maybe intracranial MUE.

Pursing Infectious Etiology

When the percentage of neutrophils in the CSF analysis is greater than 50% then the possibility of an infectious rather than immune cause for the inflammation is much higher. Typical testing when searching for infection could include PCR, serology and rarely cultures for protozoal, rickettsial, fungal, bacterial, and viral diseases. In the Mid-Atlantic region of the USA, we typically test the CSF via PCR for distemper virus, serology for *Toxoplasmosis gondi*, *Neospora caninum* and potentially *Sarcocystis neurona*, and antigen testing for *Cryptococcus* sp. as well as whole blood PCR testing for vector borne disease. Failure to improve while on antibiotics or a relapse of signs when prednisone is reduced while on antibiotic therapy is often the last step in ruling-out infection and committing to multimodal immune suppressive therapy (see below). Brain biopsy has been reported and occasionally performed in our clinic however, the procedure has risks, costs, may yield false negative or positive results and may not change the course of treatment. A recent paper describing needle guided brain biopsy had 82% of cases achieved a specific diagnosis with a 6% indirect mortality rate and 29% incidence of transient side effects (stupor, seizure, weakness and loss of proprioception).

MUE Treatment

Initial testing often reveals inflammation but does not clearly delineate between non-infectious and infectious inflammation. To address a possible infection antimicrobial therapy (clindamycin 15 mg/kg, BID, minocycline 10 mg/kg, BID +/- Fluconazole 10 mg/kg, BID) is often started while waiting for infectious disease test results. Prednisone 0.5 mg/kg, BID is also started and if signs are progressive and severe additional immune suppression could be considered with chemotherapy (Cytosine arabinoside, Lomustine, Procarbazine) and/or immune modulation with (Cyclosporine and less commonly Leflunomide, Azathioprine, or Mycophenolate). Radiation therapy has also been reported to have a positive influence of the disease course with MUE. There are many important and unanswered clinical questions revolving around what is best immunosuppressive protocol and when it is advised to stop therapy.

Steroid Therapy Insufficient

In a meta-analysis of MUE cases the median survival for dogs treated with corticosteroid plus any other immune suppressant protocol ranged from 240 to 590 days (n=96) compared with corticosteroid alone where range of median survival was 28 to 357 days (n= 43). A recent retrospective study evaluating different glucocorticoid protocols (no other immune therapy) showed survival times ranging from 2 to 2065 days – and the authors concluded that an 18 week schedule of sole prednisone therapy can be used to treat MUE. However, multiple other authors conclude that treating with immune suppressants other than prednisone will improve control of the immune condition, improve survival times, and improve quality of life for the patient by reducing steroid associated side-effects (polydipsia, polyuria, polyphagia, muscle loss, urinary tract infection, hepatotoxicity, etc.). However, which immune suppressive protocol is best is not known and there is a desperate need for randomized, blinded, controlled, prospective study of MUE to assess current and future therapies that could include (intravenous immunoglobulin, plasma exchange and even anti-viral therapy).

Once remission or improvement is achieved it can be difficult to know when to taper steroid and other immune suppressive therapy. In our experience, tapering medication can lead to relapses with poor outcomes in dogs that had a normal neurological exam. A recent paper showed that follow-up CSF analysis at 3 months can predict relapse and that tapering medication in dogs with an abnormal MRI always lead to relapse. Repeating these tests when they were previously abnormal is advised prior to the tapering or elimination of immune suppressive therapy.

Prognosis

Comparing studies is difficult due to different inclusion criteria, therapy, treatment endpoints, and lack of a prospective, controlled study. There is a recent prospective study of 39 MUE dogs treated with prednisone and then Cytosine arabinoside that provides insight into the prognosis with MUE. 13/39 (33%) died in the first 72 hours and 22/39 (56%) died within the first 52 days and the study had an overall mean survival time of 26 days (range 0-2250 days). The remaining 17 dogs that lived beyond 52 days had survivals that ranged from 562 to 2241 days (median 1616 days). Overall 12/39 (31%) dogs returned to normal and 7/39 (18%) were normal without treatment. These results can best be summarized by saying MUE can have an acute and fatal presentation up to 33% of the time and if alive at 8 weeks then survival time jumps to a median of 4 and ½ years. Among the dogs that survive more than 8 weeks, most return to normal and some can be off medication altogether.

Prognostic Indicators

One paper demonstrated that signs of high intracranial pressure (foramen magnum herniation, loss of cerebral sulci) was associated with a higher mortality. Multifocal disease and seizure have been inconsistently reported as negative prognostic indicators in MUE. A recent abstract suggested that focal brainstem disease carried best prognosis in MUE.

Seizure and the Role of Electroencephalography (EEG) in MUE

Non-convulsive seizure and non-convulsive status epilepticus (NCSE) can be present and only detectable by using EEG. In pediatrics, continuous EEG is used in patients with encephalitis, seizure and altered mentation to identify non-convulsive seizure and non-convulsive status epilepticus. Children with non-convulsive seizure have a poor outcome compared to those with the same diseases without non-convulsive seizure. We have also documented NCSE in MUE and believe that identifying and treating NCSE would improve outcome in MUE cases. NCSE should be highly suspected in MUE patients with seizure as part of the presenting complaint plus altered mentation, twitching of the ears or eyelids, sudden changes in temperature or respiratory rate, or unexplained coma. If referral for EEG is not possible, I recommend treating with Levetiracetam 60 mg/kg, IV and then potentially phenobarbital at doses of 20-40 mg/kg, divided into 6-8 mg/kg boluses until there are no abnormal movements or paroxysmal changes in vital parameters.

Steroid Responsive Meningitis-Arteritis (SRMA)

SRMA is a systemic immune disorder characterized by inflammatory lesions of the meninges and associated arteries. This disease can occur in any breed but the Bernese Mountain Dog, Boxer, Beagle, German Short and Wire Haired pointers, Weimaraner are over-represented. Clinical signs typically start at 10 months of age with a range of 6-18 months, however it has been reported in dogs as old as 7 years of age. Although histopathological changes have been noted in the heart, mediastinum, thyroid and there is an association with immune mediated polyarthritis - the clinical signs are from the meningitis (Webb). Clinical signs include neck pain and lethargy, not eating, and fever. Typical exam findings include stiff neck, short-strided gait, neck and back pain on palpation and spontaneous yelping-out or with movement. Misdiagnosis can occur because this is a sporadic disease, with non-specific, waning and waning signs that are often initially responsive to antibiotics and NSAID therapy. The diagnosis is made when inflammation is noted on CSF analysis, with most cases having a severe neutrophilic pleocytosis. The major differential diagnosis for these clinical signs is diskospondylitis which would be best identified with MRI.

A peripheral neutrophilia and elevated globulin count are inconsistently findings whereas serum C reactive protein (CRP) is elevated in all cases. CRP is an excellent biomarker for this disease because it drops to normal with resolution of disease and increases with relapse. Serum and CSF IgA concentration are increased indicating this is an immune disease, however IgA is a poor biomarker because it remains elevated, even in remission. Treatment involves high dose steroid therapy and when there is an incomplete response, relapse, or intolerable corticosteroid side effects then other immune modulators can be added-on (Azathioprine, Cyclosporine, Mycophenolate). A chronic form of the disease has been reported where there is weakness and ataxia in all 4 limbs and a mononuclear CSF analysis - it has been suggested this develops from late recognition of the disease or inadequate treatment (premature taper of therapy, too little immune suppression). Most cases return to normal. Relapse can occur in 20-60% of the cases – a higher CRP at 4 weeks is associated with multiple relapses. Although treatment durations of up to 20 months have been reported – most cases require about 6-10 months of therapy.

Conclusion

MUE is common and should be expected in any small breed dog with acute and/or progressive brain or spinal cord signs. Once diagnosed with MUE the prognosis is guarded but might be able to be improved by treating with multiple immune suppressive medications as well as anti-epileptic drugs. A return to normal is certainly possible as well as clinical remission. More study is desperately needed to determine the benefit of different treatment protocols, especially ones where multiple immune suppressive medication are given early in the course of the disease. SRMA is another example of immune mediated disease observed in medium to large breeds at about 10 months of age – if recognized early in the disease course the prognosis is excellent.

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