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Meningoencephalitis of unknown origin - the rationale for treatment

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There is a lot of confusing literature on encephalitis in dogs, confusing largely because we still do not understand the pathogenesis of this complex group of inflammatory disorders. An infectious cause of encephalitis is identified in only a very small subset of cases, and the rest of the cases were historically diagnosed with granulomatous meningoencephalitis (GME). Small breed, young adult dogs are particularly predisposed to the disease1, although it can occur in any breed and greyhounds are over-represented2. This disease is characterized histopathologically by infiltration of histiocytic and lymphocytic cells in an angiocentric distribution. Cerebrospinal fluid (CSF) evaluation reveals increased cell numbers and protein. This designation of diagnosis was problematic, as the disease could only be confirmed at necropsy, and the cases that did undergo necropsy were of course dead – the prognosis of this disease was therefore considered dismal and treatment options were limited. Clearly, as many cases respond to immunosuppression, either the disease does not carry as bad a prognosis as the literature suggested, or these animals were suffering from a different form of encephalitis. The complexity of the picture was highlighted by the emergence of a growing group of encephalitides termed the necrotizing encephalitides, classically seen in particular breeds of dog such as the Pug dog, the Maltese and the Yorkshire Terrier. These disorders were believed to be distinct from GME on histopathology, and could be further subdivided based on the distribution of the lesions into necrotizing leucoencephalitis (NLE) and necrotizing meningoencephalitis (NME). There are regions of necrosis with a mild inflammatory response associated with them and CSF analysis may be normal or only mildly inflammatory. Again, the prognosis of these diseases is reported to be extremely grave, but again, the literature largely describes dogs that have succumbed to their disease in order for a definitive diagnosis to be made.

Meningoencephalitis of Unknown Origin

Over the last decade, there has been growing recognition that simple classification of these diseases into GME, or necrotizing encephalitis is a gross oversimplification of the situation, with apparent overlap occurring in some cases, and many cases appearing to respond completely to relatively short-term treatment with drugs such as prednisone. Thus, we now have a group of diseases with clinical overlap in terms of breeds affected and prognosis (GME, NME and NLE) that may all be manifestations of the same disease, and then we have a group of diseases that appear to be responsive to prednisone therapy alone, and for which we don’t have a histopathologic description.

In order to make progress in understanding the response of encephalitis to different therapies, the term meningoencephalitis of unknown origin (MUO) has been coined. Using this definition, that does not require histopathologic examination, several case series evaluating the treatment of MUO with a variety of different agents have been published in the last 3 to 5 years. Unfortunately, most series involve fewer than 20 dogs and so it is difficult to draw definitive conclusions. However, these series are useful to describe different protocols including their possible adverse effects. Problems arise when attempts are made to compare these groups of dog with past literature. In particular, there is relatively little information on the outcome of encephalitis if treated with prednisone alone except for those cases that died and were histopathologically diagnosed with GME, MNE and NLE.

Causes of MUO

The causes of GME, necrotizing encephalitis and other MUO are unknown. Different proposed causes include infectious3, autoimmune4,5 and neoplastic conditions, and clearly there is a genetic component to the breed related disorders6. Numerous attempts have been made to identify infectious agents in affected dogs, and to date these have been unsuccessful. A possible explanation is that the disease is triggered by an infection that is rapidly eliminated but has initiated an aberrant and destructive immune response. As a result, the primary method of treatment is immunosuppression.

Immunosuppression

A wide variety of immunosuppressive agents have been used to treat MUO. The first line of therapy for many neurologists is prednisone. Protocols used vary widely but essentially involve 2 - 4 weeks at 2 - 4 mg/kg/day, tapered over the ensuing 3 – 6 months. There is remarkably little data available on how effective this treatment is for MUO in general, but there is evidence that it is not very effective in dogs that go on to have histological confirmation of GME or a necrotizing encephalitis with survival of weeks to months achieved1. This is an important point to make because the data from dogs with GME for example that have failed to respond to prednisone is now being extrapolated to compare with different therapies aimed at treating MUO. This is not a fair comparison to make and in my experience, many dogs do indeed respond well to prednisone and appear to be
cured. It is probable that these dogs have a different disease and I personally like to start treatment with prednisone alone in cases that do not have the classical signalment and presentation associated with GME.

It is now common practice to add additional drugs to prednisone aimed at suppressing the CNS immune response. Popular choices include cytosine arabinoside, cyclosporine, CCNU (lomustine), and procarbazine. Most case series describe median survivals of one to three years. Cyclophosphamide, leflunomide and azathioprine are used by some clinicians, and there is evidence that focal GME is responsive to radiation. There is evidence that GME involves a delayed type T-cell-mediated hypersensitivity. It is therefore logical to select drugs that will target T cell function. Cyclosporine A is an immunosuppressive drug that does affect T cell function by inhibiting synthesis of interleukin 2 and other cytokines. It does not cross the blood brain barrier well, but this is usually interrupted in encephalitis. It can also be argued that the T cell response is a peripheral response. A suggested dose is 3 – 15mg/kg every 12 hours to achieve a blood level of 100-300ng/ml. This can be difficult to achieve in some animals, and the drug is expensive, so addition of ketoconazole can increase blood levels by inhibiting metabolism via cytochrome P450, allowing dosing just once a day. Side effects include vomiting and diarrhea, hypertrichosis, excessive shedding and gingival hyperplasia. More serious side effects have not been recorded. The cost is a definite cause for concern for some owners. Cytosine arabinoside is a chemotherapeutic agent that crosses the blood brain barrier and inhibits DNA synthesis and repair, inhibits ribonucleotide reductase and inhibits membrane glycoprotein synthesis. A variety of dosing regimens are advocated, for example, 50mg/m² SQ twice a day for 2 days every 3 weeks (ie 200mg/m² every 3 weeks). Double this dose has been advocated, and this is a fraction of the full chemotherapeutic dose; we will use it as a CRI in dogs that are in a critical state if necessary. Side effects include myelosuppression (necessitating monitoring of CBC), GI disturbance and alopecia and dermatitis. Procarbazine has been used with similar success rates to the other 2 drugs. This MAO methylates DNA bases, causing breakage of DNA strands. It has been used at dose rates of 25-50mg/m² by mouth once a day. Side effects include myelosuppression (necessitating monitoring of CBC), nausea, vomiting and hepatic dysfunction. MAO neurotoxicity can also occur. Myelosuppression and haemorrhagic gastroenteritis have been reported in a case series treated with this drug. Lomustine, or CCNU is an alkylating agent that crosses the blood brain barrier. It has been used at a dose of 30 - 40mg/m² orally every 3 – 4 weeks. This is much lower than the dose typically used for chemotherapy (70 - 90mg/m² orally every 3 weeks), reducing the chance of developing myelosuppression and hepatic dysfunction. However, these side effects are cumulative and can still occur, and so monitoring of CBS and chemistry panel 1 week after administration is necessary.

In conclusion, there is evidence that dogs with GME, NME or NLE show improved response to immunosuppression using prednisone combined with another agent such as cyclosporine. However, there is a subset of dogs with MUO that respond to prednisone alone, but there is relatively little information published on these animals to date.

References