Steroid Responsive Meningitis–Arteritis in Dogs – A Pain in the Neck?

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ABSTRACT
Steroid responsive meningitis-arteritis (SRMA) is the most common type of meningitis in dogs and is not an uncommon disease in first opinion practice. The pathogenesis of this disease is uncertain although a consensus has been reached that this is an immune-mediated disease in which the ‘trigger’ is not known. Common presenting signs include waxing and waning cervical pain, pyrexia and lethargy. Diagnosis is based upon a combination of signalment, clinical signs and demonstration of an elevated cerebrospinal fluid (CSF) white cell count. Due to the lack of a specific disease marker, other important causes of cervical pain in young dogs that must be excluded in suspected SRMA patients include discospondylitis and atlantoaxial instability. Treatment involves immunosuppression of the patient and medication must be given over several months requiring regular monitoring. Prognosis is usually excellent provided compliance to the reported treatment protocol is maintained. Complete remission should occur in all cases although relapse is a potential problem and undesirable side-effects of medication are inevitable.

INTRODUCTION
Steroid responsive meningitis-arteritis (SRMA) in the dog is a well-recognised disease in small animal practice. This disease occurs far more frequently than bacterial meningitis and is observed worldwide in juvenile dogs. A typical presentation would be a juvenile dog (less than
two years of age) of medium-to-large-breed (often purebred) with lethargy, pyrexia, inappetance and some degree of axial skeletal pain. Axial skeletal pain is most commonly evident as a reluctance to move, a low head carriage, cervical or thoracolumbar pain and kyphosis (see Figure 1). Clinical signs can wax and wane over a period of months making detection difficult. Once a diagnosis has been made the prognosis for remission and ultimate resolution of the disease is excellent provided adherence to the treatment plan is maintained.

The aim of this article is to review the current thoughts on the diagnosis and treatment of SRMA. This article demonstrates that the diagnosis and treatment of this condition does not need to entail lengthy and complicated procedures and case management can be straightforward, cost-effective and rewarding.

Aetiology and Pathogenesis
SRMA is the most common form of meningitis occurring in young, medium-to-large-breed dogs (Tipold and Jaggy 1994, Cizinauskas et al 2000). The term SRMA is now the most universally accepted name for this disease as it describes both the histopathology and recommended treatment. Unfortunately, the numerous names to describe this disease have caused confusion and it is important to state that this disease is a different entity to granulomatous meningoencephalitis or meningoencephalitis of unknown aetiology (another disease with varied terminology; Adamo et al 2007, Shiel et al 2010, Talarico and Schatzberg 2010); diseases that tend to carry a poorer prognosis. The histopathological appearance of SRMA is characterised by an infiltration of inflammatory cells into the meninges and a vasculitis of the meningeal and coronary arteries (Meric et al 1985), hence the term ‘meningitis-arteritis’. The involvement of the coronary arteries is intriguing as this is generally subclinical although a recent report suggests myocarditis may develop secondarily to SRMA manifesting as arrhythmias and elevated troponin I (Snyder et al 2010).

The aetiology and pathogenesis of this disease is uncertain, though immunopathologic mechanisms are suspected on three accounts:
1. The presence of activated T cells – T cell activation has been identified, indicating exposure to an antigen (Tipold et al 1996), however, no bacterial or viral agent has been identified and the suspicion is that this may be a self-antigen. A Th2-mediated immune response is considered to be most likely and this immune response leads to an upregulation in the humoral immune response with subsequent production of IgA (Schwartz et al 2008).
2. Intrathecal production of IgA – the reason for the raised systemic and intrathecal IgA concentration is unknown but the phenomenon appears specific to this inflammatory disease in the dog (Schwartz et al 2008). The measurement of serum and CSF IgA has been suggested to be useful in the diagnosis of SRMA (Tipold et al 1995), particularly the chronic form, though currently IgA determination is not available as a clinical test within the UK.
3. The nature of the vascular changes – the vascular pathology is similar to that found in confirmed immune-mediated vasculitis due to immunoglobulin deposition in blood vessel walls, although the presence of immunoglobulin deposition is uncommon in SRMA and has only been reported in chronic cases (Tipold et al 1995).

Signalment
Affected dogs are usually less than two years of age (Meric et al 1985, Meric 1988, Sojnonen 1992) and typically are medium- to large-breed animals, with no apparent sex predilection. It is worth noting that dogs as old as seven years have been reported with this condition but these cases are usually of a chronic and relapsing nature and can be extremely challenging to treat. Beagles, Boxers and Bernese Mountain Dogs have been reported to be predisposed to the condition (Harcourt 1978, Poncelet et al 1993, Presthus 1991, Snyder et al 1995), and more recently the Nova Scotia Duck Tolling Retriever (Anfinsen et al 2007) and English Springer Spaniel (Lowrie et al 2009) also appear to have a predilection. However, any breed may become affected and so signalment should not be a prerequisite to the disease.

Clinical Signs
The most common clinical signs include stiffness, cervical pain, lethargy and pyrexia. Cervical pain is most commonly...
manifested by a low head carriage and arched back and, very frequently, this may be the only clinical sign present (see Figure 2). Other clinical signs that may be present from time to time include thoracolumbar pain, muscle rigidity and/or spasms (myoclonus). Neurological deficits (e.g., proprioceptive deficits and paresis) indicating involvement of the spinal cord parenchyma are usually not features of the acute disease but have been reported to become evident in cases with chronic disease: the so-called protracted form. If such changes are present, then Magnetic Resonance Imaging is required to distinguish this disease from granulomatous meningoencephalomyelitis (GME) and other inflammatory encephalitides. Clinical signs vary from peracute onset with rapid progression, through to a more chronic and insidious course with symptom-free intervals and relapse occurring as part of its natural course (Tipold and Jaggy 1994).

DIAGNOSIS

There is no specific disease marker for SRMA. Therefore, a diagnosis is only presumptive being based on a combination of clinical tests and, in the correct clinical circumstances, these laboratory findings are useful for supporting the diagnosis of SRMA. Other causes for neck pain in a young dog must be considered and ruled-out. Table 1 gives a list of some of the diseases that should be considered.


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<th>Differential Diagnosis for Cervical Pain in a Young Dog</th>
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A complete blood count commonly demonstrates evidence of a leucocytosis with left shift (i.e. band neutrophils are often identified on a peripheral smear). Biochemistry supports the presence of a systemic inflammatory response with the identification of hypoalbuminaemia. Albumin is a negative acute phase protein and so its concentration decreases in response to inflammation (Cerón et al 2005). Hyperglobulinaemia has also been reported due to the increase in serum and (CSF) concentration from immunoglobulin A production (Tipold et al 1995). The examination of CSF is arguably the most important diagnostic tool in this disease. CSF analysis is characterised by an increased white blood cell concentration (a normal CSF white blood cell concentration is considered as <5wbc/μl or 0.005 x 10⁹/L when CSF is collected from the cisterna magna) with a predominance of neutrophils in the absence of bacteria in the acute form of the disease (Figures 2 and 3A). However, as the disease progresses (and neurological deficits become apparent), mononuclear cells (macrophages, lymphocytes and monocytes) are found in the CSF and therefore the protracted form of the disease demonstrates a mixed cell pleocytosis (Figure 3B). In association with this inflammatory response, an increase in the CSF protein concentration is also to be expected (a normal CSF protein concentration is considered as <250mg/L when CSF is collected from the cisterna magna). CSF changes are sensitive to steroid administration and will be suppressed if the patient is given the drug before CSF collection – this is the reason for withholding treatment until a diagnosis is achieved. Other tests may be performed to add weight to the diagnosis. However, these tests are non-specific and only support rather than confirm the presence of disease. As previously mentioned in this article, an increase of IgA concentrations in the serum and CSF supports the diagnosis with a high sensitivity but low specificity (Tipold
et al 1995). Acute phase proteins are serum proteins produced predominantly by the liver in response to bacterial infection, trauma, neoplasia, tissue infarction, and immune-mediated inflammatory disease and, as such, are non-specific (Cerón et al, 2005). Serum C-reactive protein (CRP) and serum amyloid-A (SAA) correlate with the clinical course of SRMA with relatively increased serum and CSF concentrations at diagnosis and a resolution of clinical signs being associated with normal-to-mildly elevated serum concentrations (Bathen-Noethen et al 2009; Lowrie et al 2009). Their production is not reported to be affected by corticosteroids. Although non-specific, the magnitude of the increase in concentrations of these two proteins is such that they have a valuable role in the diagnosis of SRMA (Bathen-Noethen et al 2009; Lowrie et al 2009), particularly in cases of suspected relapse where CSF appears normal despite overt clinical signs. Finally, MRI scanning can reveal enhancement of the meninges following administration of a contrast agent (gadolinium) but the level of enhancement is often subjective and the procedure can be expensive. Therefore, it is only really justified in ruling out other diseases that can cause similar clinical signs.

**DIAGNOSIS**

The diagnosis of SRMA is based upon the signalment, history and physical examination in conjunction with an inflammatory CSF analysis, supported by haematological and biochemical values. Important differential diagnoses for cervical pain in a young adult dog are discospondylitis, cervical instability (see Figure 4) and trauma (see Table 1). A neutral, lateral cervical radiograph should, therefore, always be considered in any dog presenting with cervical pain before manipulation of the atlantoaxial joint is performed due to the possibility of instability within this region (see Figure 4). Conscious radiographs are preferable if instability is suspected, although radiographs can also be obtained under general anaesthesia provided careful handling is observed, particularly during intubation. Other differentials for inflammatory CNS disease in dogs under two years of age include protozoal diseases, although this is a rare presentation and is unlikely to present with neck pain alone. Therefore it is not always necessary in routine cases. However, when inflammatory CNS disease is present and neurological deficits are apparent then consideration should be given to the evaluation of CSF for the presence of Neospora DNA using a polymerase chain reaction (PCR) test (scanelis; Toulouse, France) (Garosi et al 2010). Alternatively, serology can be performed to assess titres for Neospora. Bacterial meningitis is uncommon in dogs and CSF culture yields a low sensitivity (Meric et al 1988, Radaelli and Platt 2002, Tipold 1995). It is therefore usually sufficient to rule out a bacterial cause by the absence of intracellular or free-living organisms on a smear and the absence of an obvious penetrating wound/infection. Other potential causes of inflammatory brain...
disease such as granulomatous GME may be ruled out during the neurological examination, although this disease can present, rarely, with neck pain as the only clinical sign. GME and other multifocal CNS diseases usually demonstrate clinical signs consistent with multifocal CNS involvement with, in particular, the brainstem and cerebral cortical structures being affected most commonly.

TREATMENT

Early diagnosis is the key to a successful outcome. A recent study recruited dogs with a prospective diagnosis of SRMA onto a strict prednisolone monotherapy regime (Lowrie et al 2009). The suggested protocol is shown in Figure 5 in which an immunosuppressive dose of prednisolone is reduced slowly over several months to the lowest dose necessary to maintain remission of clinical signs (Lowrie et al 2009). Anecdotally, it is recommended to counteract the side-effects of this drug by adding in gastroprotectants for the duration of the corticosteroid therapy, e.g. sucralfate (1-2g/dog orally q8hr) and ranitidine (2mg/kg orally q12hr). Furthermore, the owner should be informed of the potential concerns with gastrointestinal ulceration as a result of high dose steroids and be educated to observe for the presence of vomiting, inappetance, melaena or haematochezia. SRMA is associated with moderate-to-severe pain and so analgesia is frequently essential at the start of therapy. The majority of cases respond well to prednisolone at the appropriate dosage and the protocol in Figure 5 gave complete resolution of the disease in all cases that adhered to the protocol with a 20% relapse rate (Lowrie et al 2009). However, further immunosuppressive drugs may be considered in those rare cases where intractable spinal pain or relapse has been a problem, e.g. azathioprine (1.5mg/kg orally EOD). Should clinical signs of relapse occur at any stage (as is more common in the protracted form of the disease) then repeated CSF collection is indicated to confirm the nature of the relapse (acute versus chronic), followed by an increase in the prednisolone dose according to Figure 5.

Treatment with antibiotics may be necessary if the diagnosis is uncertain and if bacterial or protozoal meningitis is suspected. However, infectious meningitis is an extremely rare cause of meningitis and frequently the diagnosis is suspected based on evidence of infection elsewhere or previous trauma. If antibiotics are used then treatment should be continued until a negative CSF culture is confirmed. Anecdotal reports suggest a response to antibiotics may be seen but this is likely to be incidental because spontaneous remission is observed and clinical signs are characterised by their waxing and waning nature.

CONCLUSION

SRMA is a relatively common and readily-treated condition within small animal practice with an excellent prognosis provided the client’s expectations are addressed. The presentation of cases of SRMA is relatively consistent, with similar signalment, history and clinical signs. The response to therapy is usually very good and these cases are easy to manage once an accurate diagnosis is achieved with excellent results.

REFERENCES


**SELF ASSESSMENT QUESTIONS**

1. WHICH OF THESE STATEMENTS IS FALSE REGARDING MENINGITIS IN THE DOG?

   a) SRMA is over-represented in female dogs  
   b) Bacterial meningitis is uncommon in the dog  
   c) Generalised spinal pain is a common feature of SRMA  
   d) SRMA can occur in older dogs

2. WHICH OF THESE STATEMENTS IS TRUE REGARDING DIAGNOSIS OF SRMA IN THE DOG?

   a) CSF culture is not very sensitive at detecting bacterial infection  
   b) CSF cytology can confirm the presence of SRMA  
   c) A lumbar CSF sample should always be collected  
   d) CSF cytology is best performed following treatment

3. WHICH OF THESE STATEMENTS IS TRUE REGARDING MANAGEMENT OF SRMA IN THE DOG?

   a) Non-steroidal medication can be used in difficult cases  
   b) Prednisolone doses as high as 1-2mg/kg BID are required initially  
   c) Prednisolone can be stopped if the patient has been symptom free for one month  
   d) Azathioprine is a good first-line choice for treatment

4. WHICH OF THE FOLLOWING STATEMENTS IS FALSE?

   a) SRMA can occur without pyrexia  
   b) Relapse is a common problem with SRMA  
   c) Atlantoaxial luxation can result from SRMA  
   d) SRMA is not recognised in cats

5. WHICH OF THE FOLLOWING IS NOT NORMALLY ASSOCIATED WITH SRMA IN THE DOG?

   a) Hypercalcaemia  
   b) Neutrophilia  
   c) Hyperglobulinaemia  
   d) Raised serum IgA

**Answers:** 1: c, 2: b, 3: c, 4: d, 5: d