

## REVIEW

# An update on steroid responsive meningitis-arteritis

**Steroid responsive meningitis-arteritis (SRMA) is an immune-mediated disorder commonly recognised in dogs in small animal practice. Two different forms of SRMA may occur. The typical, acute form of SRMA is characterised by cervical rigidity, pain, pyrexia and a polymorphonuclear pleocytosis of the cerebrospinal fluid (CSF). In a less common, chronic form of SRMA, additional neurological deficits consistent with a spinal cord or a multi-focal neurological disorder may be present, often accompanied by a mononuclear CSF pleocytosis. The prognosis for young dogs in the acute stage of SRMA is relatively good with early and aggressive anti-inflammatory or immunosuppressive therapy. In more protracted, relapsing cases of SRMA the prognosis is guarded, and therapy requires more aggressive, long term immunosuppression. The complete etiopathogenesis of SRMA is unknown; however, an aberrant immune response directed against the central nervous system (CNS) is most likely. Neutrophilic pleocytosis in SRMA seems to be facilitated by chemotactic factors in the CSF and upregulation of integrins and metalloproteinases that disrupt the blood brain barrier. Upregulation of IgA, induced by a Th2 immune response, also plays a central role in the pathogenesis of SRMA.**

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*Journal of Small Animal Practice* (2010)  
51, 150–154  
DOI: 10.1111/j.1748-5827.2009.00848.x

Accepted: 24 July 2009; Published online:  
11 January 2010

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## INTRODUCTION

**Steroid responsive meningitis-arteritis (SRMA)** is also known by other names such as necrotizing vasculitis, polyarteritis, panarteritis, juvenile polyarteritis syndrome, beagle pain syndrome, corticosteroid-responsive meningitis, aseptic suppurative meningitis, sterile eitrige meningitis (sterile purulent meningitis).

## BACKGROUND

The numerous and sometimes colourful synonyms for SRMA are reflective of both the clinical and histopathologic features associated with the syndrome. However, the diverse terminology for this disorder

sometimes generates confusion among general practitioners and veterinary specialists. The name steroid responsive meningitis-arteritis is well established in the veterinary literature and best describes the pathological and clinical features of the disease, being a systemic immune disorder characterised by inflammatory lesions of the leptomeninges and the associated arteries that typically is responsive to corticosteroids (de Lahunta and Glass 2009). The disorder may occur in any breed of dog; although beagles, boxers, Bernese mountain dogs, Weimaraners and Nova Scotia duck tolling retrievers are over-represented. Age of onset typically is between 6 and 18 months with a range from 4 months to 7 years (Cizinauskas and others 2000).

## CLINICAL FEATURES

Steroid responsive meningitis-arteritis is a sporadic disorder characterised by episodes of profound cervical hyperesthesia, depression and pyrexia (de Lahunta and Glass 2009). Clinical signs result from a combined meningitis and arteritis of leptomeningeal vessels. The arteritis also may involve the vessels of the heart, mediastinum and thyroid glands (Summers and others 1995). Occasionally, SRMA occurs concurrently with immune-mediated polyarthritides (Webb and others 2002).

Two forms of SRMA exist including the "classic", acute form and the chronic, protracted form. In acute SRMA, dogs most commonly present with hyperesthesia along the vertebral column, cervical rigidity, stiff gait and fever (Tipold and Jaggy 1994). Affected animals often manifest a hunched posture with profound guarding of the head and neck, sometimes mimicking a cervical intervertebral disc protrusion. Dogs may be so painful that *any* manipulation elicits a painful response. Analysis of the cerebrospinal fluid (CSF) in acute disease reveals a marked polymorphonuclear pleocytosis in addition to an elevated protein and

variable red blood cells (Tipold and Jaggy 1994). Red blood cells may be present in CSF secondary to leakage from damaged vessels or contamination from peripheral blood. Typically, the CSF neutrophils have no toxic changes; however, in severe cases both banded and segmented neutrophils may be observed. Bacterial cultures are routinely negative. Radiographs of the cervical vertebral column are normal. Computed tomography scan or magnetic resonance imaging (MRI) may demonstrate contrast enhancement of the meninges (Fuchs and others 2000) (Fig 1a). In some dogs, the meningitis also affects the meninges of the brain and the choroid plexus (Wrzosek and others 2009) (Fig 1b).

A second, more chronic form of SRMA may be observed following relapses of acute disease and/or inadequate treatment (Tipold and Jaggy 1994). In this form of disease, meningeal fibrosis secondary to the inflammatory process may obstruct CSF flow or occlude the vasculature, rarely causing secondary hydrocephalus or ischaemia of the central nervous system (CNS) parenchyma, respectively (Summers and others 1995). Involvement of the motor and proprioceptive systems may lead to variable degrees of paresis and ataxia; other neurological signs such as menace deficits, anisocoria or strabis-

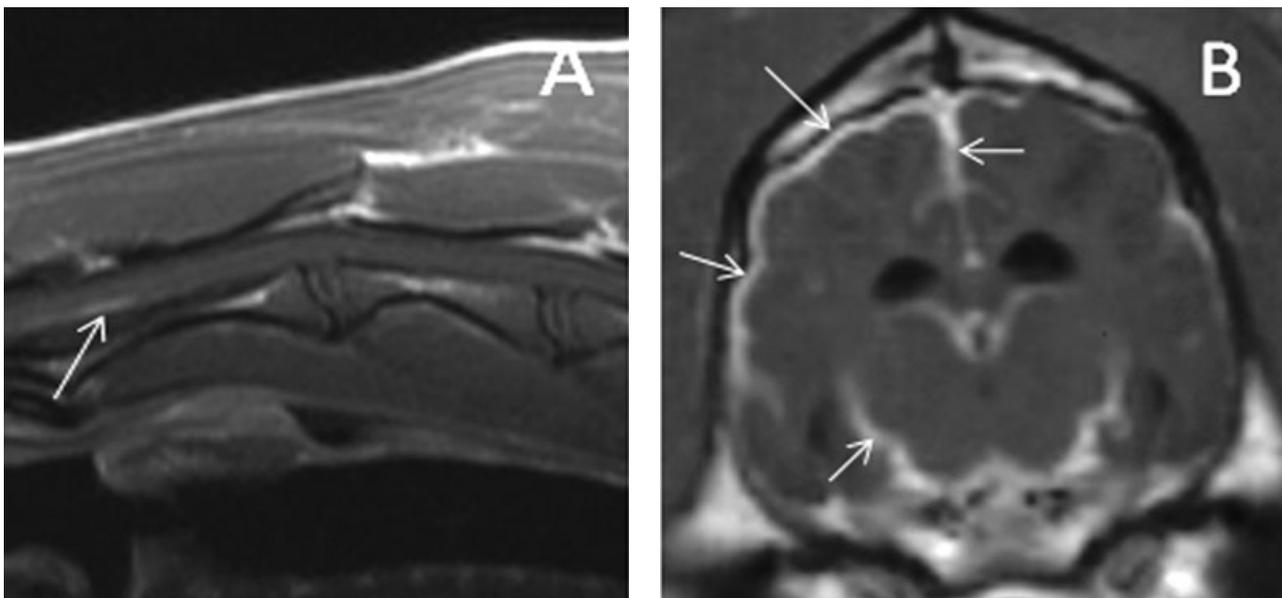
mus may occur with severe disease. The CSF in the chronic form of SRMA may be variable consisting of predominantly mononuclear cells or a mixed cell population with normal or mildly elevated total protein (Tipold and Jaggy 1994).

In both forms of SRMA, bloodwork may show a neutrophilia with a left shift, an increased erythrocyte sedimentation rate and an elevated alpha<sub>2</sub>-globulin fraction (Tipold 2000). The majority of affected dogs have elevated IgA levels in both the CSF and serum, a finding that is most likely secondary to dysregulation of the immune system (Felsburg and others 1992, Tipold 1995, Tipold and Jaggy 1994). Elevated serum and CSF IgA levels help differentiate SRMA from other idiopathic and infectious canine meningoencephalitis; however, elevated IgA levels may be associated with primary or secondary inflammation. Elevated IgM and/or IgG in the CSF also have been documented (Tipold and others 1995). More recently, acute phase proteins (APPs), including C-reactive protein (CRP) and alpha<sub>2</sub>-macroglobulin, have been shown to be elevated consistently in the serum of dogs with SRMA (Bathen-Noethen and others 2008). However, elevation of APPs is not pathognomonic for the disorder and other systemic inflammatory diseases should be

included in the differential diagnosis when present. Once SRMA has been confirmed, elevated CRP serum concentrations may be used reliably to monitor response to therapy, rather than repeated CSF collection and analyses (Bathen-Noethen and others 2008). These results were confirmed recently by Lowrie and others (2009).

## TREATMENT AND PROGNOSIS

The prognosis for SRMA is fair to good, especially in dogs with acute disease that are treated with early anti-inflammatory and/or immunosuppressive therapy. Prednisolone or prednisone immunotherapy often is required for successful treatment outcome with this disease. However, if initial signs are very mild and the neutrophilic pleocytosis is less than 200 cells/ $\mu$ l in CSF, non-steroidal-anti-inflammatory drugs therapy accompanied by careful patient monitoring may be sufficient in a subset of cases. Untreated dogs typically have a relapsing and remitting disease course. A study of 10 dogs with SRMA that received long-term treatment (4 to 20 months) showed that 8 out of 10 dogs were free of clinical signs for up to 29 months after the treatment protocol was concluded (Cizinauskas and others 2000).



**FIG 1.** (a) MRI – T1-weighted plus gadolinium, sagittal image of the cervical spinal cord; arrow denotes contrast enhancement of the meninges. (b) MRI – T1-weighted plus gadolinium, transverse image of the brain; arrows denote contrast enhancement of the meninges of the temporo-parietal lobe, falx cerebri and caudal diencephalon

The following treatment regime for a minimum of 6 months is recommended for typical cases of SRMA (Tipold 2000):

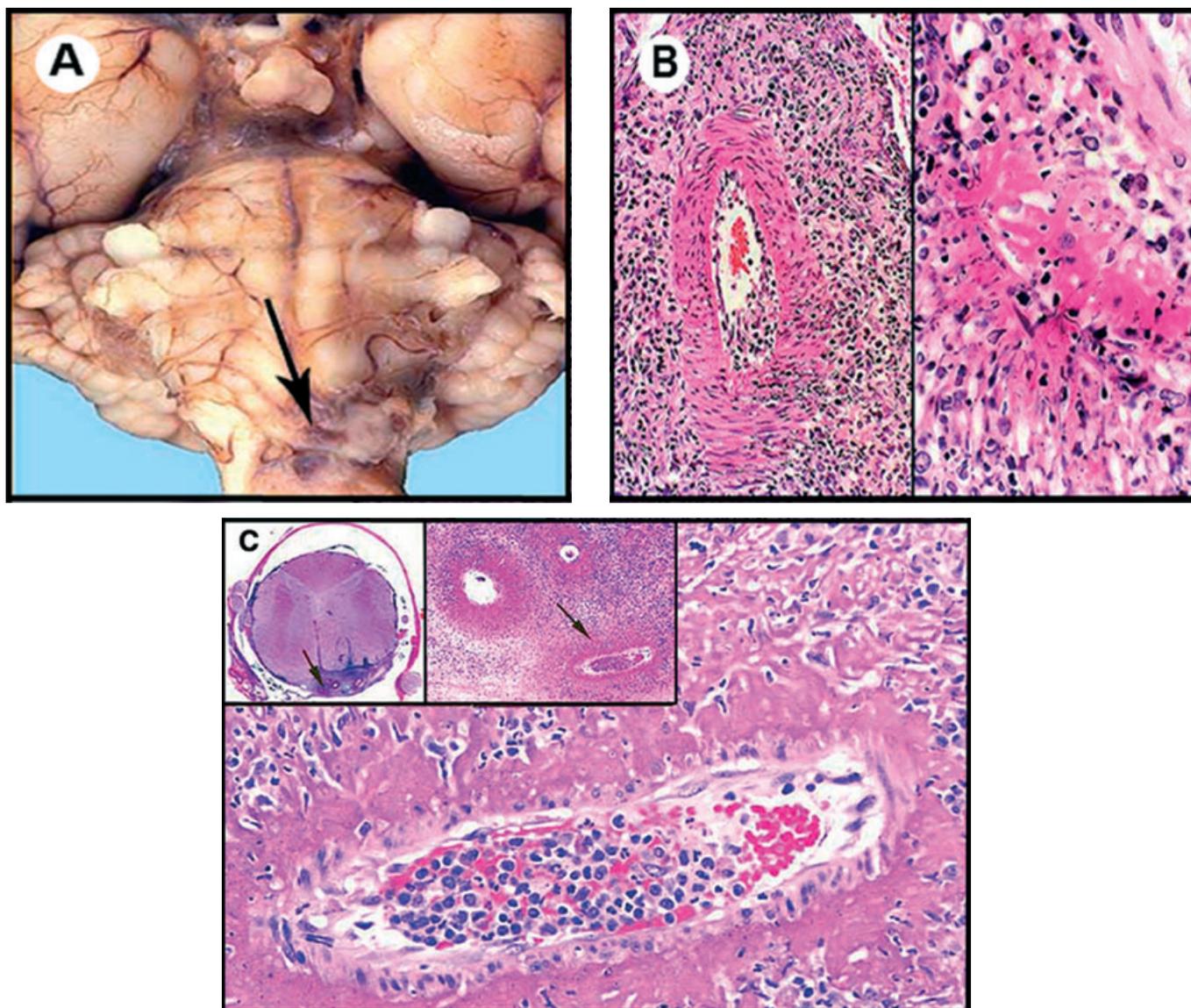
- Prednisolone or Prednisone: 4 mg/kg/day, PO or IV initially. After two days, the dose is reduced to 2 mg/kg daily for one to two weeks, followed by 1 mg/kg daily.
- Dogs are re-examined every four to six weeks; CSF analysis and haematology are repeated intermittently.
- When clinical signs and CSF are normal, the dose is reduced by half, until

a dose of 0.5 mg/kg every 48 to 72 hours is given.

- Treatment is stopped about six months after clinical examination, CSF and blood profiles are normal.

For chronic or refractory cases, the most widely utilised secondary immunosuppressive drug is azathioprine (at 1.5 mg/kg PO every 48 hours) in combination with glucocorticoids (for example, alternating each drug every other day) (Tipold 2000). Cerebrospinal fluid cell counts and serum CRP are sensitive indicators of disease

remission and have been used to monitor treatment success (Bathen-Noethen and others 2008). When the CSF and bloodwork normalise, the corticosteroid dose may be reduced progressively. It is important to note that the elevated serum and CSF IgA levels do *not* decrease to normal values during prednisolone treatment and can remain slightly increased, even after therapy is discontinued. Recurrence of clinical signs may occur due to inadequate corticosteroid treatment (both dose and duration) and may result in the protracted form of disease.



**FIG 2.** Steroid responsive meningitis-arteritis (SRMA). (a) Ventral surface of the caudal medulla with a leptomenigeal plaque (arrow) (b) High-magnification views of the prolific arterial inflammation in the cervical spinal cord leptomeninges. Neutrophils are prominent. Note the thrombosis of the arteriole. (c) Transverse section of the cervical spinal cord – low-magnification view of an inflammatory plaque in the ventral leptomeninges (arrow). In the two insets at higher magnification, note the advanced fibrinoid mural degeneration and neutrophilic infiltration

## NEUROPATHOLOGY

The characteristic lesion of SRMA is fibrinoid arteritis and leptomeningeal inflammation consisting of predominantly neutrophils and scattered lymphocytes, plasma cells and macrophages and associated necrotizing fibrinoid arteritis (Summers and others 1995) (Fig 2). Vasculitis is more common in the leptomeninges of the spinal cord than around the brain, and lesions occasionally are present in vessels in the thyroid, heart and mediastinum. Extensive leptomeningeal haemorrhages and meningeal plaques may be apparent grossly. Acute thrombosis of the vasculature may create ischemic changes in the parenchyma; in chronic lesions re-canalization of thrombi may occur (Summers and others 1995, Tipold 2000).

In the chronic form of SRMA, nerve root degeneration and rarely spinal cord infarction, secondary to rupture and haemorrhage of structurally weakened vessels, may be present (Hoff and Vandeveld 1981). Meningeal fibrosis rarely obstructs the flow of CSF and leads to secondary hydrocephalus (Tipold and others 1994). Thickened leptomeninges and less severe inflammation typically are present compared to acute disease.

## ETIOPATHOGENESIS

The exact etiopathogenesis of SRMA is unknown (Tipold 2000). Activated T cells have been demonstrated in dogs with SRMA, indicating potential contact with an antigenic stimulus; however, no bacterial or viral agents have been identified to date (Tipold and others 1996). A Th2-mediated immune response is most likely, based on the presence of high CD4:CD8a ratios and a high proportion of B cells in peripheral blood and CSF. A Th2-mediated immune response is further supported by the expression of low levels of Th1-response-related cytokines (IL-2, IFN- $\gamma$ ) and upregulation of Th2 cytokines (IL-4) in blood and CSF in dogs with the acute form of SRMA (Schwartz and others in press). This Th2-mediated immune response leads to an upregulation of the humoral immune response and excessive

IgA production (Schwartz and others 2008b).

Although autoantibodies have been demonstrated in SRMA, the antibodies are thought to be an epiphenomenon rather than actual the cause of the disease (Schulte and others 2006). Immunoglobulin deposition in blood vessel walls in SRMA lesions is rare, however focal IgA deposition has been demonstrated in chronic cases (Tipold and others 1995). Chemotactic factors including IL-8 have been identified in CSF and correlate with IgA levels (Burgener and others 1998). The constant release of chemotactic factors may explain relapsing cases and an ensuing parenchymal form of disease that occurs when steroid therapy is discontinued (Tipold and others 1994). Dogs with relapses maintain high IgA levels and coinciding chemotactic activity.

Upregulation of the integrin CD11a has been demonstrated in dogs with SRMA. Integrins are responsible for leukocyte recruitment to the CNS and CD11A upregulation may be responsible for the neutrophilic pleocytosis typically associated with SRMA. Interestingly, serum of dogs with SRMA induces CD11a upregulation on healthy neutrophils; soluble factors may be responsible for this phenomenon. It is hypothesised that CD11a expression is a key factor for neutrophil invasion into the subarachnoid space in SRMA (Schwartz and others 2008a). In addition, metalloproteinases, including MMP-2 and -9, have been shown to be upregulated in SRMA and likely disrupt the blood-brain barrier and contribute further to the neutrophilic pleocytosis (Schwartz and others 2009). Beiner has suggested oxidative stress contributes to the pathogenesis of SRMA and may lead to the protracted form of disease. Corticosteroid therapy reduces oxidative stress and may prevent the transition from the acute to chronic SRMA, either by preventing damage to the CNS vasculature or by suppressing the development of autoantigens (Beiner 2006).

Future investigations of etiopathogenesis of SRMA should include further immunological profiling, genetic studies of breeds that are over-represented for the disorder, and molecular studies of potential environmental triggers.

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