

## **Steroid-responsive meningitis-arteritis in a dog- a case report**

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### **ABSTRACT**

This paper describes in detail the case of steroid-responsive meningitis-arteritis (SRMA) in a dog. The dog was presented at the Clinic for Internal Diseases due to high fever with anorexia that lasted for five days, reluctance to move, hunched stance and stiffness that responded only moderately to antibiotics and a combination of steroidal and non-steroidal anti-inflammatory drugs administered by the referring veterinarian. The dog was fully clinically and neurologically examined and revealed fever and extreme neck pain. Complete laboratory workup and urinalysis were included. The dog underwent cerebrospinal fluid (CSF) sampling and analysis. The diagnosis of steroid-responsive meningitis-arteritis was established. Adequate therapy was instituted which resulted in clinical resolution of the disease.

**Key words:** dog, cerebrospinal fluid, steroids, meningitis-arteritis

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### **Introduction**

Many diseases in veterinary medicine lead to inflammation within the central nervous system (CNS) due to both infectious and non-infectious causes (BAGLEY, 2005). These include viral, bacterial, and fungal infections, idiopathic or immune-mediated meningitides or encephalitides, neoplasia within the CNS, traumatic causes of brain or spinal cord damage and ischemic events (WEBB and MUIR, 2000).

The hallmark of CNS inflammation is infiltration of peripheral blood leukocytes into the neuroparenchyma and its covering, resulting in various types of encephalitis and/or meningitis, sometimes associated with altered vascular integrity that leads to oedema (TIPOLD, 1995a).

The diagnosis of inflammatory diseases of the CNS can be challenging. Moreover, many results of the diagnostic evaluation of patients with inflammatory CNS diseases

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are not only non-specific but also similar, regardless of the cause of the disease, which can present a significant dilemma to clinicians (DI TERLIZZI and PLATT, 2006; HIGGINBOTHAM et al., 2007).

Analysis of cerebrospinal fluid (CSF) is one of the best diagnostic procedures to evaluate the brain and spinal cord and to establish the exact diagnosis (CHRISMAN, 1992; KIŠ et al., 2003; DI TERLIZZI and PLATT, 2008). The collection of CSF is not without risk and patients need to be selected with care if maximum benefit is to be gained from its use. A CSF examination is indicated in any animal with certain or suspected neurological disease in which a diagnosis is not readily apparent, including dogs and cats with a suspected intracranial disorder as the cause of a seizure disorder, with fever and axial pain, or with progressive signs of deteriorating mentation (CHRISMAN, 1992; DI TERLIZZI and PLATT, 2008).

Steroid-responsive meningitis-arteritis (SRMA) is an immunopathological condition in dogs with frequent relapses of clinical signs. The disease is characterised histopathologically by infiltration of inflammatory cells into the meninges and by inflammatory-stenotic lesions of meningeal arteries (MERIC et al., 1985; CIZINAUSKAS et al., 2000; GANDINI et al., 2003). It has been shown that excessive immunoglobulin A (Ig A) production plays a central role in the pathogenesis of this condition (TIPOLD and JAGGY, 1994; CIZINAUSKAS et al., 2000). The disease appears in two clinical forms: the more typical acute form and the less common atypical (or chronic) form. The acute condition is characterised by fever, pain and cervical rigidity, pleocytosis with polymorphonuclear cells in the CSF. The more protracted atypical form is associated with additional neurological deficits and mixed or mononuclear pleocytosis in the CSF (TIPOLD 1995b; CIZINAUSKAS et al., 2000; GANDINI et al., 2003). Glucocorticoids play a major role in the treatment of SRMA (MUNANA, 1996). The possible mechanisms of the action are inhibition of cytokine, prostaglandin and leukotriene production, inhibition of invasion of inflammatory cells through the blood-brain barrier and reduction of tissue damage (CIZINAUSKAS et al., 2000). The best treatment is long-term prednisolone as described by TIPOLD and JAGGY (1994).

The aim of this paper is to present a case of steroid-responsive meningitis-arteritis diagnosed by CSF analysis in a dog in Croatia. To the authors' knowledge this is the first report of SRMA in Croatia.

### **Materials and methods**

A nine month-old female Bernese mountain dog was presented at the Clinic for Internal Diseases, due to high fever with anorexia that lasted for five days, reluctance to move, stiffness and defensive behaviour. The dog was pre-treated with amoxicilline

with clavulanic acid and a combination of steroidal and non-steroidal anti-inflammatory drugs without significant improvement. The dog was fully clinically and neurologically examined and laboratory work-up was also included.

Blood samples for haematological and biochemical analyses were taken from vena cephalica. Haematological analysis was performed using a Baker System Serrono 9120 CP haematologic counter.

Biochemical analyses were performed in serum after blood centrifugation at 1200 g for ten minutes. Creatinine, blood urea nitrogen (BUN), glucose, total serum proteins, albumine, calcium and activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP),  $\gamma$ -glutamyl transferase (GGT) and serum creatine kinase (CK) were determined using an Olympus AU 600 biochemical autoanalyser. Analyses were performed with standard methods and the manufacturer's original reagents (Olympus). Urinalysis consisted of dipstick examination and sediment evaluation.

After the first clinical and neurological examination, CSF sampling had to be postponed since the dog was under therapy with steroidal anti-inflammatory drugs administered by the referring veterinarian which could influence the composition of CSF. Prior to CSF sampling, five days after the first examination, the dog again underwent a second thorough clinical, neurological and laboratory examination.

Food was withheld for 12 hours prior to CSF sampling, which was performed under general anaesthesia. After administration of atropine (0.02 mg/kg, i.v.) (Atropin, Belupo, Koprivnica, Croatia) and diazepam (0.25 mg/kg i.v.) (Apaurin, Krka, Slovenia), the dog was anesthetized by administration of 2.5% thiopental sodium (Thiopental, 0,5 g, Nycomed, Roskilde, Denmark) intravenously, at first 6 mg/kg was given rapidly as a bolus and one additional increment of the remainder was given to effect light endotracheal intubation. CSF was taken by cisternal puncture in lateral recumbency using a spinal needle (Spinal Needle, FM GmbH, Wächtersbach, Germany) 22G  $\times$  38 mm (KIŠ et al., 2003; DI TERLIZZI and PLATT, 2008). CSF was examined immediately after puncture for protein content (Pandy reaction), cell count and cell differentiation. One part of the sample was preserved separately in sterile tube for bacteriological examination.

## Results

On physical examination the most striking extraneural sign was severe hyperthermia (40.7 °C), other than that no physical abnormalities were found. Neurological examination revealed a characteristic hunched stance, neck rigidity and extreme pain with minimal neck manipulation. Postural reactions including proprioception were normal, as were spinal reflexes and tests of cranial nerves. Haematology and biochemistry values at

presentation and before CSF sampling are presented in Tables 1 and 2. Results of dipstick and sediment examination of the urine were in the reference range. Results of liquor analysis are presented in Table 3.

Table 1. Results of haematological analysis in dog with steroid-responsive meningitis-arteritis

Haematological values	Dog		Standard values Kraft and Dürr (2005)
	1 <sup>st</sup>	2 <sup>nd</sup>	
Red blood cells ( $\times 10^{12}$ /l)	7	6.6	5.5-8.5
Hemoglobin (g/l)	172	156	132-190
PCV (%)	47	44	40-55
MCV (fl)	67	67	60-77
Platelets (G/l)	272	257	150-500
WBC ( $\times 10^9$ /l)	34.5	35.5	6-15
Neutrophils (%)	65	61	55-75
Bands (%)	1	-	0-4
Lymphocytes (%)	28	39	13-30
Monocytes (%)	2	-	0-4
Eosinophils (%)	4	-	0-6

Table 2. Serum biochemistry values in dog with steroid-responsive meningitis-arteritis

Biochemical findings	Dog		Standard values Kraft and Dürr (2005)
	1 <sup>st</sup>	2 <sup>nd</sup>	
Blood urea nitrogen	5.4	4.8	3.3-8.3 mmol/L
Creatinine	96	103	35-106 $\mu$ mol/L
Aspartate aminotransferaze (AST)	113	147	- 44 U/L
Alanine aminotransferaze (ALT)	44	57	- 55 U/L
Alkaline phosphatase (AP)	217	247	- 108 U/L
$\gamma$ -glutamyltransferase(GGT)	3	2	- 5 U/L
Creatine kinase (CK)	1646	1690	- 90 IU/L
Glucose	5.5	4.9	3.9-6.7 mmol/L
Total serum proteins	69	68	54-75 g/L
Albumins	29	29	25-44 g/L
Calcium	2.7	2.5	2.3-3.0 mmol/L

Table 3. Results of CSF analysis in dog with steroid-responsive meningitis-arteritis

Parameter	CSF findings	Standard values Jaggy (2005)
Clearness and colour	Slight turbidity	clear
Number of cells/ $\mu$ l	1014	0-8
Pandy reaction	+++	negative
Cyhtological findings	78% neutrophils, 22% mononuclear cells	Mononuclear cells

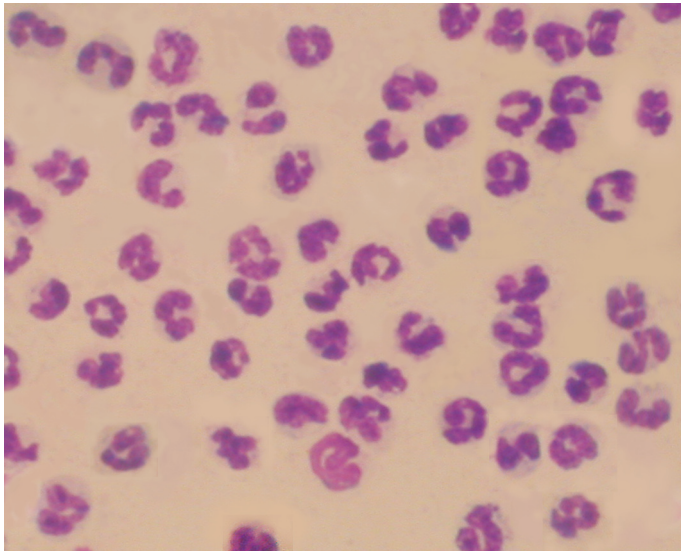


Fig. 1. Cytological slide of cerebrospinal fluid in dog with steroid-responsive meningitis-arteritis, a detail with predominant neutrophils, May-Grünwald Giemsa staining;  $\times 100$ .

On cytomorphologic examination toxic neutrophils and bacteria were not found (Fig. 1). Bacteriological examination was negative.

### Discussion

Inflammatory diseases form an important core of diseases of the central nervous system (CNS) (THOMAS, 1998). Approximately 10% of neurological cases in dogs are due to infectious or inflammatory disease and 15% of these are due to SRMA (TIPOLD, 1995a).

In our case the dog had typical signs of SRMA. It is well known that the disease is often reported in Beagles, Bernese Mountain Dogs, Boxers, German Short-Haired Pointers and only sporadically in other breeds (IRVING and CHRISMAN, 1990). Affected animals are mostly young adults between 8 and 18 months (MUÑANA, 1996), as it was the case with our dog.

The only haematological abnormality found in this case was marked leukocytosis. Although haematological analyses in clinical investigation of the neurological disease serve only to provide evidence of systemic infection and although many primary CNS inflammatory diseases do not produce a systemic response and therefore negative findings do not rule out infectious disease of the CNS, positive findings can prove useful (LORENZ and KORNEGAY, 2004). SRMA is one neurological diseases in which most affected dogs reveal leukocytosis with a left shift (CIZINAUSKAS et al., 2000), whereas in our dog only the leukocytosis was present.

Biochemical parameters had to be included in the clinical work up of the patient to exclude other possible causes of presenting clinical signs. In our case only the activity of creatine kinase (CK) was considerably increased. This can be linked to similar conditions already described known as necrotizing vasculitis, polyarteritis, canine pain syndrome and canine juvenile polyarteritis syndrome which include the same disease, described histopathologically as vasculitis of the central nervous system (SCOTT-MONCRIEFF et al., 1992). In some reports (SNYDER et al., 1995) extraneural lesions were also reported. It might be that this was the case with our dog too.

In 71% of dogs with inflammatory CNS diseases a high protein concentration is found (TIPOLD, 1995a). The Pandy reaction in our dog was positive. It is one of the oldest CSF techniques and is sensitive in detecting increased protein levels and requires only a few microliters of CSF; this was advantageous since part of the sample had to be preserved for bacteriological examination. However, the Pandy test is not specific for certain proteins, but it is a sensitive indicator for the presence of organic central nervous system disease (BICHSEL et al., 1984). This was also found to be true for our dog. In our dog CSF pleiocytosis was present. CSF pleiocytosis is often indicative of encephalitis but is also seen in several other conditions (BICHSEL et al., 1984). Pleocytosis is usually found in 88% of dogs with inflammatory diseases. Usually pleocytosis is mild to moderate. Extremely high cell numbers are frequently found in dogs with SRMA, bacterial meningitis and granulomatous meningoencephalitis (TIPOLD, 1995b).

The clinical diagnosis was based on a combination of clinical findings, laboratory tests and CSF analysis results. The intrathecal as well as systemic IgA concentration is increased in SRMA (TIPOLD and JAGGY, 1994; TIPOLD 1995a; TIPOLD 1995b). The determination of IgA levels is very useful for differential diagnostics since this phenomenon is not found

in other inflammatory and infectious diseases of the CNS (SCHULTE et al., 2006), but unfortunately, we were not able to determine IgA in the serum or CSF. It seems that this production as well as the marked response to steroids indicates that the immune response in SRMA is in part specifically directed towards the CNS (TIPOLD et al., 1994; TIPOLD et al., 1999; SCHULTE et al., 2006). Inability to isolate bacteria or viruses also confirms this hypothesis (TIPOLD et al., 1995).

Based upon CSF findings, the most important differential diagnosis which should be excluded prior treatment is bacterial meningitis. It occurs in dogs with no breed, age or sex predilection and clinical signs in some patients can include neck pain and pyrexia. Complete blood count (CBC) in these patients often reveals neutrophilic leukocytosis and CSF analysis is abnormal in 93% of patients having increased protein content and increased white blood cell number, with a prevalence of neutrophils in most dogs (RADAELLI and PLATT, 2002). The most important clinical difference between bacterial meningitis and SRMA is the lack of neurological localizing symptoms on neurological examination as well as no identifiable bacteria or toxic neutrophils on cytomorphological examination of the CSF and negative bacteriological examination. Based upon the typical neurological signs with no localization, signalment and CSF findings with negative bacteriological findings the diagnosis of SRMA was established. Other differential diagnoses include encephalitides with neutrophilia in the CNS such as protozoal diseases and granulomatous meningoencephalitis (GME), but they have more profound neurological deficits due to invasive lesions and are not limited to the meninges. If the dog in our case had had the chronic form of the SRMA, it would be more difficult to diagnose the disease since a larger list of possible differential diagnoses should be considered. It would include all viral encephalitides, GME, protozoal infections and neoplasms (SARFATY et al., 1986).

The prognosis is relatively good in young dogs in the acute stage of the disease when the disease is treated aggressively. In more protracted cases, relapses are frequent, and the prognosis is guarded. In those cases therapy is more complicated and time consuming. About 60% of dogs with SRMA are cured after immunosuppressive treatment. Treatment is not tolerated in approximately 5% of dogs (GANDINI et al., 2003).

The dog was treated with an immunosuppressive, long-term corticosteroid therapy (TIPOLD and JAGGY, 1994; CIZINAUSKAS et al., 2000). Prednisolone was given at an initial dosage of 4 mg/kg per day. After two days, the dosage was reduced to 2 mg/kg per day for two weeks, followed by 1 mg/kg/day for one month. Since there were no signs of recurrence, the dog was maintained on 0.5 mg/kg/day for one month and on 0.5 mg/kg every alternate day for another month (GANDINI et al., 2003). The dog improved soon after institution of the therapy. Approximately 6 months after cessation of the therapy the dog relapsed and underwent the reported therapy schedule once more. The dog is now two months without therapy and without clinical signs.

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**KIŠ, I., J. FORŠEK, V. MATIJATKO, N. KUČER, K. ŠIMONJI: Meningitis-arteritis u kuje izlječiv steroidima - prikaz slučaja. *Vet. arhiv* 78, 529-538, 2008.**

**SAŽETAK**

Rad prikazuje slučaj meningitis-arteritisa u kuje izlječivog steroidima. Kuja je dovedena na Kliniku za unutarnje bolesti zbog višednevne visoke temperature, inapetencije, nevoljkog kretanja, ukočenoga hoda, zgrbljenoga stava i promijenjenoga ponašanja. Kuja je pokazivala samo djelomično kliničko poboljšanje na liječenje antibioticima te steroidnim i nesteroidnim protuupalnim lijekovima. Životinja je klinički i neurološki pregledana. Ustanovljena je povišena temperatura te izrazita bolnost pri pasivnom pokretanju vrata. Učinjene su

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laboratorijske pretrage krvi i mokraće. Nakon toga učinjena je punkcija likvora te njegova analiza. Postavljena je dijagnoza meningitis-arteritisa koji reagira na steroide. Započeto je odgovarajuće liječenje koje je završilo izlječenjem.

**Cljučne riječi:** pas, likvor, meningitis-arteritis koji reagira na steroide

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