

VETERINARSKI ARHIV 80 (5), 611-626, 2010

Systemic inflammatory response syndrome and multiple organ dysfunction syndrome in canine babesiosis

Vesna Matijatko^{1*}, Ivana Kiš¹, Marin Torti¹, Mirna Brkljačić¹, Renata Barić Rafaj², Zdravko Žvorc¹, and Vladimir Mrljak¹

¹ Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia

² Department of Chemistry and Biochemistry, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia

MATIJATKO, V., I. KIŠ, M. TORTI, M. BRKLJAČIĆ, R. BARIĆ RAFAJ, Z. ŽVORC, V. MRLJAK: Systemic inflammatory response syndrome and multiple organ dysfunction syndrome in canine babesiosis. Vet. arhiv 80, 611-626, 2010.

ABSTRACT

Canine babesiosis caused by *Babesia canis canis* is one of the commonest canine diseases in Croatia, especially in the area of capital city, Zagreb. Babesiosis is a multi-system disease and multiple organ dysfunction syndrome (MODS) develops from systemic inflammatory response syndrome (SIRS), which is a hallmark of babesiosis. Therefore, the purpose of this study was to conduct detailed research of the incidence of SIRS and MODS as well as organ systems involvement in a large number of dogs naturally infected with *B. canis canis* in Croatia. Out of 332 dogs with canine babesiosis, 226 dogs (68 percent) fulfilled the SIRS criteria and were considered as SIRS positive. Among them 151 dogs (67%) fulfilled two SIRS criteria, 66 dogs (29%) fulfilled three criteria and only 9 dogs (4%) fulfilled all four SIRS criteria. Thirty-three dogs (10%) fulfilled the MODS criteria. Among them 22 dogs (66%) had two organ involvement, 10 dogs (31%) had three organ involvement and in only 1 dog (3%) four organ dysfunction was present. The incidence of organ involvement in MODS was as follows: renal dysfunction (30/33), liver dysfunction (20/33), muscle involvement (19/33), lung dysfunction (16/33), cerebral involvement (3/33). Among MODS positive dogs, 22 dogs died and 11 dogs survived babesiosis. In dogs with two organ involvement, survival was 45%, in dogs with three organ involvement survival was 10%, while in the group with four organ dysfunction mortality was 100%. It can be concluded that in cases of canine babesiosis caused by *B. canis canis*, in which MODS developed, an unfavourable outcome should be taken into consideration.

Key words: babesiosis, dog, systemic inflammatory response syndrome, multiple organ dysfunction syndrome

*Corresponding author:

Dr. Vesna Matijatko, DVM, PhD, Assistant Professor, Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb, Heinzelova 55, 10000 Zagreb, Croatia, Phone: +385 1 2390 343, E-mail: vesna.matijatko@vef.hr

Introduction

Canine babesiosis is a tick borne disease caused by the intra-erythrocytic protozoan parasites from the genus *Babesia*. In Europe it is caused by the *Babesia canis*, *Babesia gibsoni*, *Babesia conradae* and *Babesia microti-like* species, provisionally classified as *Theileria annae* (UILENBERG et al., 1989; TABOADA and MERCHANT, 1991; ZAHLER et al., 2000; CAMACHO et al., 2001). There are three antigenically different subspecies of *B. canis*: *B. canis canis*, *B. canis vogeli* and *B. canis rossi* (UILENBERG et al., 1989). Canine babesiosis caused by *B. canis canis* is a very common cause of morbidity of dogs in Croatia, especially in the area of the capital city, Zagreb (CACCIÒ et al., 2002; MATIJATKO et al., 2007; BECK et al., 2009; BRKLJAČIĆ et al., 2009).

On the basis of clinical manifestation, the disease can be classified as uncomplicated or complicated (LOBETTI, 1998; JACOBSON, 2006). The typical signs of uncomplicated babesiosis are pale mucous membranes, fever, anorexia, depression, splenomegaly and water hammer pulse (TABOADA and MERCHANT, 1991). The clinical manifestation of complicated form is variable and includes acute renal failure, cerebral babesiosis, coagulopathy, icterus and hepatopathy, immune-mediated haemolytic anaemia (IMHA), peracute babesiosis, acute respiratory distress syndrome (ARDS), haemoconcentration and shock (LOBETTI, 1998).

The different clinical manifestations of canine babesiosis are difficult to relate only to haemolysis. In recent years more and more authors are proposing a uniform mechanism that leads to different clinical manifestations (JACOBSON and CLARK, 1994; LOBETTI, 1998; MATIJATKO et al., 2007). It is based on the hypothesis that systemic inflammatory response syndrome (SIRS) and consequent multiple organ dysfunction syndrome (MODS) provide the underlying pathophysiological mechanism within which unrelated aspects of babesiosis form a recognisable pattern. Since babesiosis, like human malaria caused by *Plasmodium falciparum*, can be classified as “protozoal sepsis” (BONE et al., 1992; JACOBSON et al., 2002), it is likely that the inflammatory mechanisms in this disease are similar to those of other septic conditions clinically characterised by SIRS and MODS.

SIRS is the clinical expression of the acute phase reaction (PANNEN and ROBOTHAM, 1995; NYSTRÖM, 1998) and is considered to be present if two or more of the following occur: tachycardia, tachypnoea (or respiratory alkalosis), hypothermia or hyperthermia, leukocytosis or leukopenia and neutrophilic left shift (CIPOLLE, 1993). The presence of SIRS and MODS has been described in canine babesiosis caused by *B. canis rossi*, which is the most pathogenic subspecies of *B. canis* (WELZL et al., 2001). In Croatia the vast majority of canine babesiosis are caused by *B. canis canis* (CACCIÒ et al., 2002; BECK et al., 2009; BRKLJAČIĆ et al., 2009), which is the most common causative organism in Europe as well (CACCIÒ et al., 2002; DUH et al., 2004; FÖLDVÁRI et al., 2005; SOBCZYK et al., 2005).

Therefore, the purpose of this study was to conduct research into the incidence of SIRS and MODS as well as organ systems involvement on large number of dogs naturally infected with *B. canis canis* in Croatia. Moreover, it has been proven that different babesia isolates vary in their virulence and pathogenicity and cause different forms of canine babesiosis (SCHETTERS et al., 1997). As a result, it is interesting to investigate clinical forms of canine babesiosis in every region.

Materials and methods

The records of all patients with developed complicated babesiosis on admission that were treated at the Clinic for Internal Diseases of the Faculty of Veterinary Medicine, Zagreb from January 2000 to December 2007, were reviewed retrospectively. Babesiosis was diagnosed by demonstration of parasites within the infected erythrocytes in Romanowsky-stained thin blood smears. All the dogs with confirmed babesiosis and complete laboratory and clinical data necessary for SIRS and MODS classification, which were SIRS positive and showed at least two organ dysfunctions, were included in this study. All the dogs that fulfilled MODS criteria but were SIRS negative were excluded from the study.

Dogs were clinically examined, which included neurological examination and determination of small animal coma scale score in non hypoglycaemic animals (OLIVER et al., 1997). Thoracic radiography was performed for all the dyspnoeic dogs. The blood samples for analysis were collected from the cephalic vein. The samples were placed in tubes with EDTA for haematological analysis and tubes with no anticoagulant, which were centrifuged at 1200 x g prior to biochemical analysis. White blood cell count (WBC), platelet count and haematocrit (HCT) were determined using an automatic haematology analyzer (System 9120; Serono Baker Diagnostic) while serum creatinine, alanine aminotransferase (ALT), alkaline phosphatase (AP), creatine phosphokinase (CPK), glucose and serum bilirubin were determined using a biochemical autoanalyser Olympus AU 600. Analyses were performed using standard methods and original reagents of the manufacturer (Olympus).

The SIRS criteria used in this study were established on the basis of the criteria proposed by OKANO et al. (2002). The animal was classified as SIRS positive if two or more of the following criteria were fulfilled: body temperature higher then 39.7 °C or lower then 37.8 °C, heart rate more then 160 beats per minute, respiration rate more then 40 breaths per minute and WBC count less than $4 \times 10^9/L$ or more than $12 \times 10^9/L$ or more than 10 percent band neutrophils.

The animal was classified as MODS positive if two or more of the following criteria were fulfilled: renal dysfunction (serum creatinine more than 180 $\mu\text{mol/L}$ - reference values 44-140 $\mu\text{mol/L}$), liver dysfunction (alanine aminotransferase, ALT, more than

176 U/L - reference value less than 88 U/L, and alkaline phosphatase, AP, more than 360 U/L - reference value less than 156 U/L), central nervous system dysfunction (a modified Glasgow coma scale score less than 9) (SHORES, 1989; WELZL et al., 2001), respiratory system dysfunction (radiographic pulmonary oedema, dyspnoea or blood/tinged frothy nasal discharge), muscular involvement (creatin phosphokinase, CPK, more than 600 U/L - reference value less than 160 U/L). We included bilirubin value greater than 100 µmol/L (reference value 1.7-8.6 µmol/L) as an additional criterion for liver dysfunction (WEISER, 1992).

One dose (6 mg/kg) of imidocarb dipropionat (Imizol[®], Schering-Plough) was administered to all the dogs subcutaneously on the day of admission. Additional treatment consisted of various fluids (hydroxyethyl starch and crystalloids in twenty six dogs; human albumin, hydroxyethyl starch and crystalloids in two dogs whose albumin concentration were below 20 g/L; whole blood transfusion in a dog whose haematocrit was 7%). The dog that developed DIC received additionally fresh plasma. All the dogs that were dyspnoeic or had radiographic signs of pulmonary oedema received oxygen supplementation via intranasal tubes or oxygen cage.

The prognostic values of the presence of SIRS and MODS were tested using the ROC curve analysis. Values of area under the curve higher than 0.75 were considered good, while values of the area under the curve higher than 0.92 and 0.97 were considered very good and excellent respectively.

Results

Three hundred and thirty-two cases fulfilled the selection criteria for canine babesiosis and were included in the study. The study population comprised fifty-one pure breeds and mixed breed dogs (Table 1). There were 196 males and 136 female dogs.

Two hundred and twenty-six dogs (68 percent) fulfilled the SIRS criteria and were considered as SIRS positive. Among them 151 dogs (67%) fulfilled two SIRS criteria, 66 dogs (29%) fulfilled three criteria and only 9 dogs (4%) fulfilled all four SIRS criteria (Fig. 1). The prognostic value of SIRS is shown in Fig. 2.

Thirty-three dogs (10%) fulfilled the MODS criteria (Fig. 3). Among them 22 dogs (66%) had two organ involvement, 10 dogs (31%) had three organ involvement and in only 1 dog (3%) four organ dysfunction was present (Fig. 4). The most common organ system involvement in MODS was: renal dysfunction (30/33), liver dysfunction (20/33), muscle involvement (19/33), lung dysfunction (16/33), cerebral involvement (3/33) (Fig. 5).

Among MODS positive dogs, 22 dogs died and 11 dogs survived babesiosis (Table 2). In dogs with two affected organs survival was 45%, in dogs with three organ involvement survival was 10%. The only dog with four affected organs died (Fig. 6).

Table 1. Breeds of dogs included in the study

Breed	No. of patients
Mixed	93
Rottweiler	23
English cocker spaniel	21
Labrador retriever	21
German shepherd	20
Poodle	14
Golden retriever	14
Pekinese	13
Alaskan malamut	7
Doberman	7
German boxer	7
Collie	7
Belgian shepherd	6
Siberian husky	6
Irish setter	6
Toy poodle	5
Staffordshire bullterrier	4
Yugoslavian shepherd dog Sharplanina	4
Giant schnauzer	4
West highland white terrier	4
Bernese dog	3
Beauceron	3
Dalmatian	2
English bulldog	2
Croatian sheepdog	2
Yorkshire terrier	2
Maltese dog	2
Great dane	2
German pointer shorthaired	2
Miniature pinscher	2
Bobtail	2
Alpine dachsbracke, Argentinean dog, Basset, St. Bernard dog, Beagle, Boston terrier, Chow-Chow, English setter, Epagneul breton, Fox terrier, Miniature schnauzer, Schnauzer, Shorthaired dachshund, Wirehaired dachshund, Cavalier king Charles spaniel, Neapolitan mastiff, German hunting terrier, Pit bull terrier, Pointer, Pomeranian, Bosnian and Herzegovinian - Croatian shepherd dog, Welsh terrier	1 (total 22)
Total number of patients	332

Table 2. Comparison of mortality rate for MODS and non-MODS canine babesiosis

Criteria	Survivors	Non-survivors
MODS positive	33%	67%
MODS negative	95%	5%

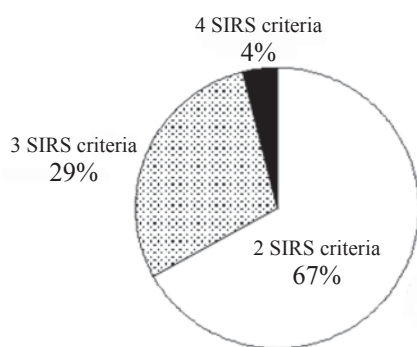


Fig. 1. Number of positive criteria in dogs that developed SIRS due to canine babesiosis

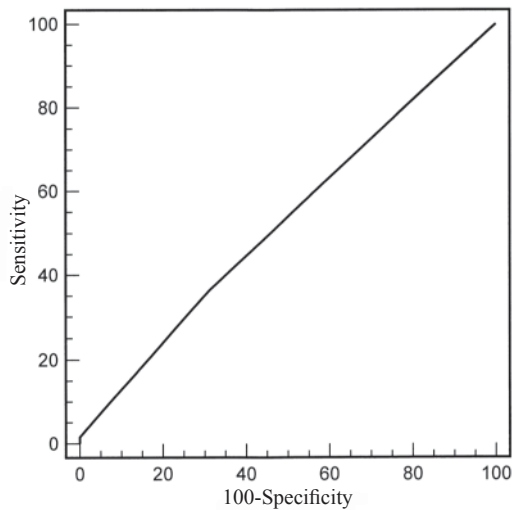


Fig. 2. ROC curve analysis for prognostic value of SIRS in predicting outcome

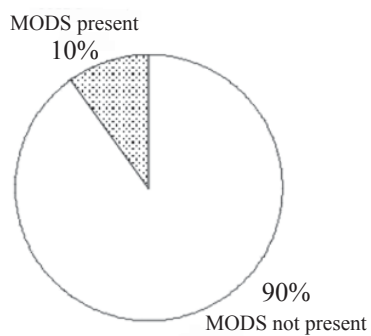


Fig. 3. Percentage of dogs that developed MODS due to canine babesiosis.

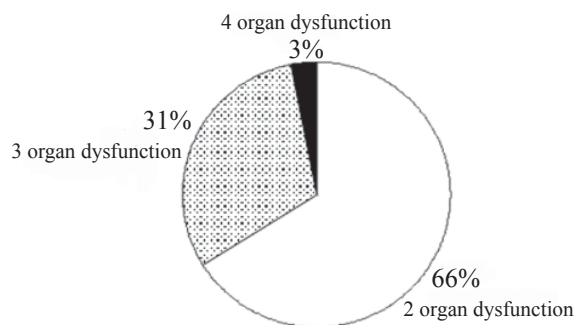


Fig. 4. Number of affected organs in MODS positive dogs with canine babesiosis.

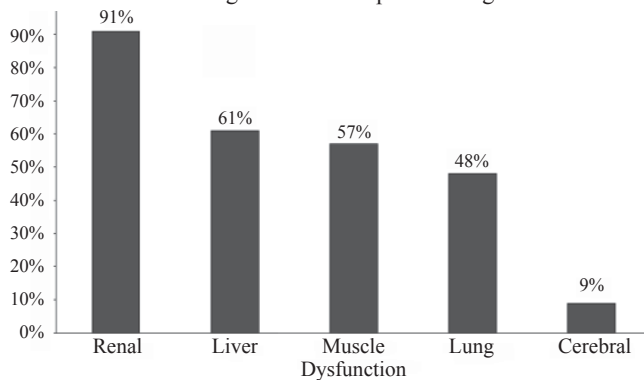


Fig. 5. Distribution of organ involvement in dogs that developed MODS due to acute canine babesiosis

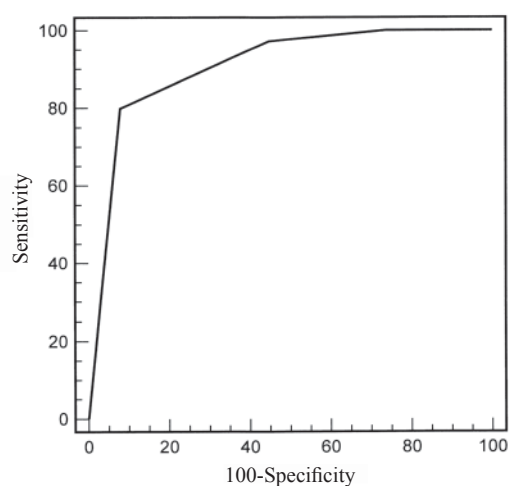


Fig. 6. ROC curve analysis for prognostic value of MODS in predicting outcome

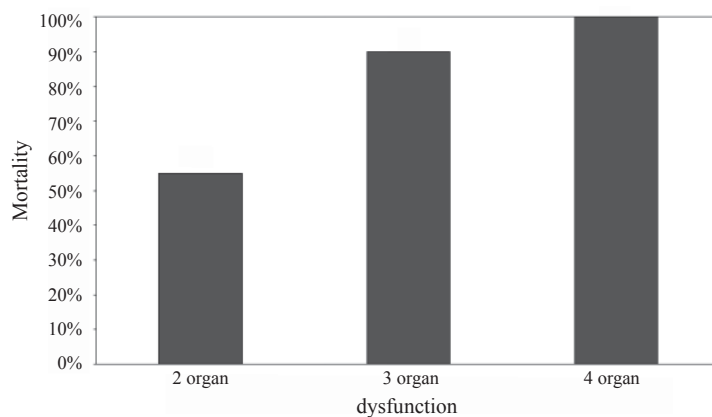


Fig. 7. Comparison of the mortality rates for different numbers of failed organs in dogs with canine babesiosis

The presence of SIRS showed poor prognostic value while the presence of MODS showed excellent prognostic value in predicting the outcome of babesiosis (Figs. 2, 7).

Discussion

This study included a large number of dogs of more than 50 breeds. On the basis of hospital records, the breed distribution roughly represents the popularity of breeds in

Croatia. Also, in this study there were 196 males and 136 females. This ratio between male and female dogs with babesiosis could be explained by the predominance of male dogs in Croatia.

Complicated babesiosis includes manifestations that cannot be directly explained by haemolysis but appear to be the result of the host inflammatory response to the parasite, rather than the parasite itself. This is thought to explain similarities between various conditions such as babesiosis, malaria, sepsis, multiple trauma, and burns (JACOBSON and CLARK, 1994). These similarities have provoked scientists to change the original definition of sepsis being caused exclusively by bacteria. According to the current definition, sepsis may be caused by viruses, fungi and parasites. It is now considered that sepsis is SIRS with the proven presence of an infectious agent in the blood (BONE et al., 1992).

SIRS is frequently present in canine babesiosis (WELZL et al., 2001). Since the SIRS criteria in human medicine were established through the process of consensus conference (BONE et al., 1992), the SIRS concept has been widely used to judge prognosis in emergency and intensive care fields because of its simplicity and usefulness (SUN and AIKAWA, 1999). In veterinary, as in human, medicine different authors have proposed different SIRS criteria (PURVIS and KIRBY, 1994; HAUPTMAN et al., 1997; BRADY and OTTO, 2001; OKANO et al., 2002). The cut-off values for the SIRS criteria are a major issue in veterinary medicine since normal values for temperature, heart rate and respiratory rate vary in dogs due to the significant variations in their size (HOUSTON and RADOSTITS, 2000). The results of a study conducted by WELZL et al. (2001) strongly indicate that the criteria used to identify SIRS in veterinary medicine need revision, as a significant number of dogs with MODS were not recognised as SIRS positive. In this study the SIRS criteria proposed by OKANO et al. (2002) were used, because this is a tested model that has showed the best prognostic value in canine babesiosis of all SIRS criteria models used in veterinary medicine (KIŠ, 2007). In our study we also identified dogs that were SIRS negative but fulfilled the MODS criteria. Our results showed that the presence of SIRS was not useful in predicting outcome (area under the curve 0.53) (Fig. 2). Since our study was designed to review the data in concordance with the established SIRS and MODS criteria, and to compare them with the results already published of the prevalence and main features of MODS in canine babesiosis in other countries, these dogs were excluded from this study. Thus, our study also confirms the necessity of revision of SIRS and MODS criteria in veterinary medicine.

Babesiosis is a multi-system disease (JACOBSON, 2006). Multiple organ dysfunction syndrome is documented in canine babesiosis caused by *B. canis rossi* (WELZL et al., 2001). GORIS et al. (1985) hypothesized that MODS develops as the consequence of dysregulation of proinflammatory and anti-inflammatory mechanisms resulting in overwhelming auto-destructive inflammation. Ninety-one percent of MODS positive

dogs in this study showed signs of renal dysfunction, 61% of them had liver dysfunction, 57% had muscle damage, 48% showed lung damage and 9% had cerebral involvement. In contrast WELZL et al. (2001) reported that the most frequently organ involved during *B. canis rossi* infection was the liver, then kidney, muscles, lungs and the central nervous system. The differences between the aforementioned study and our study are that in our study renal dysfunction was more frequent than liver dysfunction, and the incidence of muscle damage was higher. The higher incidence of liver dysfunction in the study conducted by WELZL et al. (2001) may be the result of the diversity of illnesses caused by *B. canis rossi* and *B. canis canis*. In the aforementioned study, bilirubin as a liver dysfunction criterion was not included because bilirubin was not considered sensitive enough in a haemolytic disease such as babesiosis. JACOBSON and CLARK (1994) reported that hepatic impairment should always be considered in an icteric dog. WEISER (1992) reported that bilirubin values greater than 100 $\mu\text{mol/L}$ should be suggestive of coexisting hepatic dysfunction in haemolytic disease. MATIJATKO et al (2009) in their study of septic shock in babesiosis found very high levels of bilirubin which was not attributable to haemolysis alone, because they found the highest levels of bilirubin in non-anaemic and slightly anaemic dogs. Based on all these results, we decided to include serum bilirubin values higher than 100 $\mu\text{mol/L}$ as an indicator of liver dysfunction.

The exceptionally high incidence of renal dysfunction (90 percent of dogs) could be explained by the fact that patients with MODS are also hypotensive, and hypotension causes poor tissue perfusion, especially detrimental to renal tissue (BONE et al., 1992; BAGSHAW and BELLOMO, 2006; ALDRICH, 2007; MATIJATKO et al., 2009). Renal dysfunction could also be explained by the cytokine release. Injecting the tumour necrosis factor (TNF) into rats (TRACEY et al., 1986) or dogs (TRACEY et al., 1987) produces acute renal tubular necrosis, the very lesions seen in canine babesiosis (MAEGRAITH et al., 1957; LOBETTI et al., 1996). However, pre-renal azotaemia, with no structural renal damage, can also lead to elevated serum creatinine concentrations. This cannot be ruled out entirely because this is a retrospective study which limits numerous extrapolations. Nevertheless, post-mortem examination revealed damage to the kidneys: parenchymal dystrophy and/or acute tubular necrosis in seven dogs.

Inflammatory mediators can also cause acute lung injury. The number of patients that showed lung dysfunction in this study was very similar to the results obtained by WELZL et al. (2001). The most frequent sign of lung involvement noted was dyspnoea which in some cases progressed into pulmonary oedema.

WELZL et al. (2001) stated that: “muscle damage followed an interesting pattern representing the lowest percentage of all affected organs in the single-organ failure group, but rising steeply to second place in triple-organ failure”. Since in our investigation, most

patients had two or three-organ involvement, our results are in fact in concordance with the aforementioned study.

As in the study conducted by WELZL et al. (2001) CNS involvement was also the rarest complication seen in our study. Hypoglycaemia was excluded in cases with neurological signs since neurological signs often attributed to cerebral babesiosis could also be caused by hypoglycaemia, which has been reported in dogs with babesiosis caused by *Babesia canis rossi* (KELLER et al., 2004; NEL et al., 2004). Cerebral babesiosis is a well known form of babesiosis in South Africa (PURCHASE, 1947; BOTHA, 1964; JACOBSON, 2006). It is interesting that CNS involvement was only present in our study as a part of MODS and not as single organ damage as noted in the South African form of babesiosis (WELZL et al., 2001).

There are several proposed mechanisms that can promote the development of MODS. The first mechanism is related to the parasite. High parasitaemias are unlikely to be the sole trigger of MODS in canine babesiosis considering the fact that some dogs with low parasitemias developed septic shock (BÖHM et al., 2006; MATIJATKO et al., 2009). The second proposed mechanism is tissue anoxia caused by lysis of erythrocytes (JACOBSON and CLARK, 1994). This hypothesis is in direct contradiction with the results obtained by REYERS et al. (1998) because in their study of canine babesiosis the highest mortality rate was in the group of non-anaemic dogs. Another possible mechanism is excessive host inflammatory response to the parasite due to overproduction of inflammatory mediators. The arguments for the cytokine theory mechanism are supported by the fact that acute phase protein production is increased in canine babesiosis (MATIJATKO et al., 2007) and acute phase protein synthesis is a direct consequence of increased cytokine production (BAUMANN and GAULDIE, 1994; STEEL and WHITEHEAD, 1994; PANNEN and ROBOTHAM, 1995; GABAY and KUSHNER, 1999; CERON et al., 2005). On the other hand, the concentration of CRP did not show prognostic value, because it was not associated with outcome in babesiosis caused by *B. canis rossi* (KÖSTER et al., 2009). The last fact that has to be taken into consideration is that it has been proven that different strains of *B. canis canis* and *B. rossi* cause different clinical forms of babesiosis (CARCY et al., 2006; MATJILA et al., 2009). Moreover, different babesia strains can be directly linked with the outcome and prognosis of babesiosis (MATJILA et al., 2009). Since the strains of *B. canis canis* were not determined in this study, we cannot rule out that the development of MODS is not the consequence of infection by a highly pathogenic strain of *Babesia canis canis*.

The mortality in MODS is very high and in human medicine can reach 80-100% (CIPOLLE, 1993). Mortality increases with the number of failing organs and in cases with two failing organs mortality is 60-70%, when there are three failing organs present it is above 90%, while in cases with four failing organs mortality is 100% (FRY et al., 1980). In

our study mortality in the group with two failing organs was 55%, in group with 3 failing organs the mortality was 95%. There was only one animal with four affected organs so we cannot comment meaningfully on mortality in this group. It is very interesting to mention the results of a study of canine babesiosis caused by *B. canis rossi* in which was concluded that development of MODS does not influence the outcome of this disease (WELZL et al, 2001). Since we have determined that the development of MODS has an excellent prognostic value of outcome (area under the curve 0.92, Fig. 6), our results are in direct opposition with the above mentioned study, but are in concordance with other studies of MODS (FRY et al., 1980; CIPOLLE, 1993; MATIJATKO et al., 2009). The possible explanation for this difference between canine babesiosis studies could be the high incidence of hypotension and consequential development of septic shock in babesiosis in Croatia (MATIJATKO et al., 2009), which is apparently not the case in the South African form of babesiosis caused by *B. canis rossi* (JACOBSON et al., 2000). However, babesiosis caused by *B. canis rossi* and babesiosis caused by *B. canis canis* are considered to be different diseases, with different clinical manifestations (SCHETTERS et al., 1997). Moreover, even in babesiosis caused by the same subspecies of *Babesia* the clinical manifestation could be different if caused by different strains (MATJILA et al., 2009). Therefore, it is necessary to determine the strains of *B. canis canis* in order to comment on the results better.

Finally, it may be concluded that in cases of canine babesiosis caused by *B. canis canis*, in which MODS developed, an unfavourable outcome should be taken into consideration. We can also conclude that in MODS the mortality rate increases with the number of failing organs. The results in this study are original and we present them in order to document the presence of MODS in canine babesiosis in Croatia as well as to investigate the incidence of MODS and the incidence of organ involvement in MODS due to canine babesiosis caused by *B. canis canis*. However, since this is a retrospective study, we believe that a prospective case-controlled study should be undertaken in order to minimise all the possible flaws of retrospective studies. As a further step in the investigation of canine babesiosis in Croatia, it is of great importance to determine the strains of *B. canis canis* and their pathogenicity in order to link them to complications and outcome of babesiosis.

References

- ALDRICH, J. (2007): Assessment and diagnosis of shock. In: BSAVA Manual of Canine and Feline Emergency and Critical Care Medicine. (King, L. D., A. Boag, Eds.). BSAVA, Gloucester. pp. 17-29.
- BAGSHAW, S. M., R. BELLOMO (2006): Fluid resuscitation and the septic kidney. *Curr. Opin. Crit. Care* 12, 527-530.
- BAUMAN, H., J. GAULDIE (1994): The acute phase response. *Immunol. Today* 15, 74-80.

V. Matijatko et al.: Systemic inflammatory response syndrome and multiple organ dysfunction syndrome in canine babesiosis

- BECK R., L. VOJTA, V. MRLJAK, A. MARINCULIĆ, A. BECK, T. ŽIVIČNJAK, M. S. CACCIO (2009): Diversity of *Babesia* and *Theileria* species in symptomatic and asymptomatic dogs in Croatia. *Int. J. Parasitol.* 39, 843 - 848.
- BONE, R. C., R. A. BALK, F. B. CERRA, R. P. DELLINGER, A. M. W. FEIN, A. KNAUS (1992): Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. ACCP/SCCM consensus conference committee. *Chest* 101, 1644-1655.
- BOTHA H. (1964): The cerebral form of babesiosis in dogs. *J. S. Afr. Vet. Assoc.* 35, 27-28.
- BÖHM, M., A. L. LEISEWITZ, P. N. THOMPSON, J. P. SCHOEMANN (2006): Capillary and venous *Babesia canis rossi* parasitemias and circulatory compromise. *Vet. Parasitol.* 141, 18-29.
- BRADY, C. A., C. M. OTTO (2001): Systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction. *Vet. Clin. North Am. Small Anim. Pract.* 31, 1147-1162.
- BRKLJAČIĆ M., V. MATIJATKO, I. KIŠ, N. KUČER, J. FORŠEK, R. BARIĆ RAFAJ, D. GRDEN, M. TORTI, I. MAYER, V. MRLJAK (2010): Molecular evidence of natural infection with *Babesia canis canis* in Croatia. *Acta Vet. Hung.* 58, 39-46.
- CACCIÒ, S. M., B. ANTUNOVIC, A. MORETTI, V. MANGILI, A. MARINCULIC, R. RAFAJ BARIC, S. B. SLEMENDA, N. J. PIENIAZEK (2002): Molecular characterization of *Babesia canis canis* and *Babesia canis vogeli* from naturally infected European dogs. *Vet. Parasitol.* 106, 285-292.
- CAMACHO A. T., E. PALLAS, J. J. GESTAL, F. J. GUITIAN, A. S. OLMEDA, H. K. GOETHERT, S. R. TELFORD (2001): Infection of dogs in north-west Spain with a *Babesia microti* - like agent. *Vet. Rec.* 149, 552-555.
- CARCY, B., E. PRECIGOUT, T. SCHETTERS, A. GORENFLOT (2006): Genetic basis for GPI-anchor merozoite surface antigen polymorphism of *Babesia* and resulting antigenic diversity. *Vet. Parasitol.* 138, 33-49.
- CERON, J. J., P. D. ECKERSALL, S. MARTINEZ- SUBIELA (2005): Acute phase proteins in dogs and cats: current knowledge and future perspectives. *Vet. Clin. Pathol.* 34, 85-99.
- CIPOLLE, M. D., M. D. PASQUALE, F. B. CERRA (1993): Secondary organ disfunction. *Crit. Care Clin.* 9, 261-298.
- DUH, D., N. TOZON, M. PETROVEC, K. STRAŠEK, T. AVŠIČ-ŽUPANC (2004): Canine babesiosis in Slovenia: Molecular evidence of *Babesia canis canis* and *Babesia canis vogeli*. *Vet. Res.* 35, 363-368.
- FÖLDVÁRI, G., E. HELL, R. FARKAS (2005): *Babesia canis canis* in dogs from Hungary: detection by PCR and sequencing. *Vet. Parasitol.* 127, 221-226.
- FRY, D. E., L. PEARLSTEIN, R. L. FULTON, H. C. POLK (1980): Multiple system organ failure: the role of uncontrolled infection. *Arch. Surg.* 115, 136-140.
- GABAY, C., I. KUSHNER (1999): Acute-phase proteins and other systemic responses to inflammation. *N. Engl. J. Med.* 340, 448-454.

- GORIS, R. J., T. P. BOCKHORST, J. K. NUYTINEK, J. S. GIMBRERE (1985): Multiple-organ failure. Generalized autodestructive inflammation? *Arch. Surg.* 120, 1109-1115.
- HAUPTMAN, J. G., R. WALSHAW, N. B. OLIVIER (1997): Evaluation of the sensitivity and specificity of diagnostic criteria for sepsis in dogs. *Vet. Surg.* 26, 393-397.
- HOUSTON, D. M., O. M. RADOSTITS (2000): The Clinical Examination. In: *Veterinary Clinical Examination and Diagnosis.* (Radostits, O. M., I. G. Mayhew, D. M. Houston, Eds.). W.B. Saunders. London. pp. 91-124.
- JACOBSON, L. S. (2006): The South African form of severe and complicated canine babesiosis: Clinical advances 1994-2004. *Vet. Parasitol.* 138, 126-139.
- JACOBSON, L. S., I. CLARK (1994): The pathophysiology of canine babesiosis: New approaches to an old puzzle. *J. S. Afr. Vet. Assoc.* 65, 134-145.
- JACOBSON, L. S., R. G. LOBETTI, P. BECKER, F. REYES, T. WAUGHAN-SCOTT (2002): Nitric oxid metabolites in naturally occurring canine babesiosis. *Vet. Parasitol.* 104, 27-41.
- KELLER, N., L. S. JACOBSON, M. NEL, M. DE CLERQ, P. N. THOMPSON, J. P. SCHOEMAN (2004): Prevalence and risk factors of hypoglycemia in virulent canine babesiosis. *J. Vet. Intern. Med.* 18, 265-270.
- KIŠ, I. (2007): Primjena kliničkog sustava bodovanja u procjeni prognoze ishoda babezioze u pasa (Development of Clinical Scoring System for Outcome Prediction in Canine Babesiosis). Dissertation. Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia.
- KÖSTER S., M. VAN SCHOOR, A. GODDARD, P. N. THOMPSON, P. T. MATJILA, M. KJELGAARD-HANSEN (2009): C-reactive protein in canine babesiosis caused by *Babesia rossi* and its association with outcome. *J. S. Afr. Vet. Assoc.* 80, 87-91.
- LOBETTI, R. G., F. REYERS, J. W. NESBIT (1996): The comparative role of haemoglobinaemia and hypoxia in the development of canine babesial nephropathy. *J. S. Afr. Vet. Assoc.* 67, 188-198.
- LOBETTI, R. G. (1998): Canine babesiosis. *Comp. Cont. Educ. Pract. Vet.* 20, 418-431.
- MAEGRAITH, B., H. M. GILLES, K. DEVAKUL (1957): Pathological processes in *Babesia canis* infections. *Z. Tropenmed. Parasit.* 8, 485-514.
- MATIJATKO, V., V. MRLJAK, I. KIŠ, N. KUČER, J. FORŠEK, T. ŽIVIČNJAK, Ž. ROMIĆ, Z. ŠIMEC, J. J. CERON (2007): Evidence of an acute phase response in dogs naturally infected with *Babesia canis*. *Vet. Parasitol.* 144, 242-250.
- MATIJATKO, V., I. KIŠ, M. TORTI, M. BRKLJAČIĆ, N. KUČER, R. BARIĆ RAFAJ, D. GRDEN, T. ŽIVIČNJAK, V. MRLJAK (2009): Septic shock in canine babesiosis. *Vet. Parasitol.* 162, 263-270.
- MATJILA, P. T., B. CARCY, A. L. LEISEWITZ, T. SCHETTERS, F. JONGEJAN, A. GORENFLOT, B. L. PENZHORN (2009): Preliminary evaluation of the BrEMA1 gene as a tool for associating *Babesia rossi* genotypes and clinical manifestation of canine Babesiosis. *J. Clin. Microbiol.* 47, 3586-3592.
- NEL, M., R. G. LOBETTI, N. KELLER, P. N. THOMPSON (2004): Prognostic value of blood lactate, blood glucose and hematocrit in canine babesiosis. *J. Vet. Intern. Med.* 18, 471-476.

- NYSTRÖM, P. O. (1998): The systemic inflammatory response syndrome: definitions and aetiology. *J. Antimicrob. Chemother.* 41, Suppl. A, 1-7.
- OKANO, S., M. YOSHIDA, U. FUKUSHIMA, S. HIGUCHI, K. TAKASE, M. HAGIO (2002): Usefulness of systemic inflammatory response syndrome criteria as an index for prognosis judgement. *Vet. Rec.* 150, 245-246.
- OLIVER, J. E., M. D. LORENZ, J. N. KORNEGAY (1997): Stupor or coma. In: *Handbook of Veterinary neurology* (Oliver, J. E., M. D. Lorenz, J. N. Kornegay). W. B. Saunders. Philadelphia. pp. 287-312.
- PANNEN, B. H. J., J. L. ROBOTHAM (1995): The acute-phase response. *New Horizons* 3, 183-197.
- PURCHASE, H. S. (1947): Cerebral babesiosis in dogs. *Vet. Rec.* 59, 269-270.
- PURVIS, D., R. KIRBY (1994): Systemic inflammatory response syndrome: septic shock. *Vet. Clin. North Am. Small Anim. Pract.* 24, 1225-1247.
- REYERS, F., A. L. LEISEWITZ, R. G. LOBETTI, R. J. MILNER, L. S. JACOBSON (1998): Canine babesiosis in South Africa: more than one disease. Does this serve as a model for falciparum malaria? *Ann. Trop. Med. Parasitol.* 92, 503-511.
- SCHETTERS, T. P. M., K. MOUBRI, E. PRECIGOUT, J. KLEUSKENS, N. C. SCHOLTES, A. GORENFLOT (1997): Different *Babesia canis* isolates, different diseases. *Parasitol.* 115, 485-493.
- SHORES, A. (1989): Craniocerebral trauma. In: *Current Veterinary Therapy X*. (Kirk, R. W., Ed.) WB Saunders Co. Philadelphia. pp. 847-853.
- SOBCZYK, A. S., G. KOTOMSKI, P. GORSKI, H. WEDRYCHOWICZ (2005): Usefulness of touch-down PCR assay for the diagnosis of atypical cases of *Babesia canis canis* infections in dogs. *Bull. Vet. Inst. Pulawy.* 49, 407-410.
- STEEL, D. M., A. S. WHITEHEAD (1994): The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. *Immunol. Today* 15, 81-87.
- SUN, D., N. AIKAWA (1999): The natural history of the systemic inflammatory response syndrome and the evaluation of SIRS criteria as a predictor of severity in patients hospitalised through emergency services. *The Keio J. Med.* 48, 28-37.
- TABOADA, J., S. R. MERCHANT (1991): Babesiosis of companion animals and man. *Vet. Clin. North Am. Small Anim. Pract.* 21, 103-123.
- TRACEY, K. J., B. BEUTLER, S. F. LOWRY, J. MERRYWEATHER, S. WOLPE, I. W. MILSARK, R. J. HARIRI, T. J. FAHEY, A. ZENTELLA, J. D. ALBERT, G. T. SHIRES, A. CERAMI (1986): Shock and tissue injury induced by recombinant human cachectin. *Science* 234, 470-474.
- TRACEY, K. J., S. F. LOWRY, T. J. FAHEY, J. D. ALBERT, Y. FONG, D. HESSE, B. BEUTLER, K. R. MANOGUE, S. CALVANO, H. WEI, A. CERAMI, G. T. SHIRES (1987): Cachectin-tumor necrosis factor induces lethal shock and stress hormone responses in the dog. *Surg. Gynecol. Obstet.* 164, 415-422.

V. Matijatko et al.: Systemic inflammatory response syndrome and multiple organ dysfunction syndrome in canine babesiosis

- UILENBERG, G., F. F. J. FRANSSEN, N. M. PERRIE (1989): Three groups of *Babesia canis* distinguished and a proposal for nomenclature. *Vet. Q.* 11, 33-40.
- WEISER, M. G. (1992): Diagnosis of immunohemolytic disease. *Semin. Vet. Med. Surg.* 7, 311-314.
- WELZL, C., A., L. LEISEWITZ, L. S. JACOBSON, T. VAUGHAN-SCOTT, E. MYBURGH (2001): Systemic inflammatory response syndrome and multiple-organ damage/dysfunction in complicated canine babesiosis. *J. S. Afr. Vet. Assoc.* 72, 158-162.
- ZAHLER, M., H. RINDER, E. SCHEIN, R. GOTHE (2000): Detection of a new pathogenic *Babesia microti*-like species in dogs. *Vet. Parasitol.* 89, 241-248.

Received: 4 November 2008

Accepted: 9 July 2010

MATIJATKO, V., I. KIŠ, M. TORTI, M. BRKLJAČIĆ, R. BARIĆ RAFAJ, Z. ŽVORC, V. MRLJAK: Sindrom sustavnoga upalnoga odgovora i sindrom višestrukoga zatajenja organa u pasa s babeziozom. *Vet. arhiv* 80, 611-626, 2010.

SAŽETAK

Babezioza uzrokovana praživotinjom *Babesia canis canis* jedna je od najčešćih bolesti pasa u Hrvatskoj, osobito u području oko glavnoga grada Zagreba. Babezioza je bolest koja zahvaća više organskih sustava, a sindrom višestrukoga zatajenja organa (engl. multiple organ dysfunction syndrome) razvija se iz sindroma sustavnog upalnog odgovora (engl. systemic inflammatory response syndrome), koji je karakterističan za babeziozu. Cilj ovoga rada bio je proučiti pojavnost sindroma sustavnog upalnog odgovora i sindroma višestrukoga zatajenja organa na velikom broju pasa koji boluju od babezioze, kao i učestalost zahvaćenosti pojedinih organskih sustava u sindromu višestrukoga zatajenja organa. Od 332 pasa s potvrđenom babeziozom 226 pasa (68%) razvilo je sindrom sustavnog upalnog odgovora. Od njih je 151 pas (67%) ispunio 2 kriterija, 66 pasa (29%) ispunilo je 3 kriterija, dok su u 9 pasa (4%) bila ispunjena sva četiri kriterija. Trideset i tri psa ispunila su kriterije za sindrom višestrukoga zatajenja organa. Od njih su 22 psa (66%) imala zahvaćena po dva organska sustava, 10 pasa (31%) imalo je zahvaćena tri organska sustava, dok je samo 1 pas (3%) imao zahvaćena četiri organska sustava. Najčešće zahvaćeni organski sustavi u sindromu višestrukoga zatajenja organa bili su: uropoetski sustav (30/33), jetra (20/33), mišićje (19/33), dišni sustav (16/33) i središnji živčani sustav (3/33). Od pasa koji su razvili sindrom višestrukoga zatajenja organa 22 su uginula dok ih je 11 preživjelo babeziozu. Preživljavanje pasa u kojih su bila zahvaćena 2 organska sustava bilo je 45%, sa zahvaćena 3 organska sustava bilo je 10%, dok je smrtnost sa zahvaćena 4 organska sustava iznosila 100%. Na temelju rezultata se može zaključiti da je razvoj sindroma višestrukoga zatajenja organa u babeziozi pasa prognostički značajan i da u slučaju da se sindrom razvije raste i vjerojatnost nepovoljnog ishoda.

Ključne riječi: babezioza, pas, sindrom sustavnog upalnog odgovora, sindrom višestrukoga zatajenja organa
