Prof. Łukasz Adaszek, PhD, DVM*, Piotr Teodorowski, DVM **, Oliwier Teodorowski, DVM **
**Department of Epizootiology and Clinic of Infectious Diseases, Faculty of Veterinary Medicine, University of Life Sciences in Lublin, ul Głęboka 30, 20-612 Lublin*
***Teodorowscy Veterinary Clinic, ul. Żwirki i Wigury 5, 43-190 Mikołów*

Cerebral babesiosis

– use of the BrainActiv Balance® (Vetfood) dietary supplement in dogs during convalescence

Abstract
Canine babesiosis is a common and clinically significant tick-borne disease caused by hematozoan parasites of the genus Babesia. The pathophysiology of canine babesiosis has been extensively studied but many questions remain unanswered, especially regarding the diversity of disease manifestations. This paper offers a description of cerebral babesiosis cases in 8 dogs. The efficacy of the BrainActiv Balance diet supplement in a supportive therapy of this form of the disease is discussed

Keywords
Babesia canis, dogs, BrainActiv Balance

Canine babesiosis is a tick-borne disease. Its aetiological agents are intraerythrocytic protozoa of the genus Babesia (family Babesidae, order Piroplasmida, phylum Apicomplexa) (1). Two groups of these pathogenic parasites for dogs are distinguished based on their cellular morphology: larger ones of about 3–5 µm, called B. canis, and smaller ones of 1–3 µm, i.e. B. gibsoni (2). Analysis of the 18S RNA, Bc28, 5.8S, hsp70, and cytochrome B genes has shown that in fact numerous Babesia species are aetiological agents of canine babesiosis. The following species have been identified among small piroplasms: Babesia conradae, Babesia microti-like, also known as Theileria annae, the 'Spanish isolate', and Theileria spp. (3,4,5). Large piroplasms include three species that were initially considered to be subspecies of B. canis – B. rossi, B. canis and B. vogeli, as well as a large Babesia species that was relatively recently detected in dogs in the United States and has not yet been named (6,7,8,9). All of them have the same cell morphology, but they differ in terms of geographic range, genetic structure, and virulence. These protozoa are also transmitted by different species of ticks (9,10,11).

Thus far only Babesia canis has been detected in dogs in Poland (12,13,14,15,16). The course of the disease it induces may be uncomplicated and manifested by anaemia, or complicated, resulting in multiple organ failure and a systemic inflammatory response. Complicated babesiosis is noted much more frequently in the records of veterinary clinics. This is because patients with this infection are generally reported to veterinarians after they have been ill for several days, when their clinical symptoms have become more severe (complications have appeared).

Cases of the cerebral form of babesiosis in dogs have recently been increasingly noted (17,18,19). The aetiology of this form of the disease is not fully known. Its development may be due to disseminated intravascular coagulation (DIC), extravasations in the brain (20), or hypoxia appearing as a consequence of erythrocyte aggregation in the capillaries (21).

Disturbances in blood flow seem to play an important role in the pathogenesis of the cerebral form of babesiosis (22).

This form of the disease is difficult to treat. Management of sick animals involves causal treatment – combating the protozoan infection with imidocarb, fluid therapy, and symptomatic treatment of neurological disorders. The animals' recovery may take many weeks, so it is essential to ensure appropriate rehabilitation and diet during convalescence.

The aim of the study was to determine the effect of administration of the dietary supplement BrainActiv Balance® (Vetfood) on the speed of recovery of dogs with cerebral babesiosis.

Observations

The subjects of the study were 8 male, mixed-breed dogs (aged 2-7 years) with a body weight of 7-10 kg, in which babesiosis had been confirmed by microscopic examination and/or molecular testing (PCR) (Fig. 1).

The animals were brought to the clinic with symptoms of apathy and depression (n=8) as well as dark urine (n=8), accompanied by neurological symptoms in the form of seizures, impaired consciousness (n=8), loss of balance (n=6), strabismus (n=3) and opisthotonos (n=2).

Haematological examination of all animals with confirmed babesiosis revealed thrombocytopaenia (PLT < 200 x109) and leukopaenia (WBC < 6 x109). In five dogs haematocrit had fallen below 37% (lower limit) and erythrocytes to below 5.5 x1012 (lower limit).

Causal treatment of all animals involved subcutaneous administration of imidocarb dipropionate in the amount of 5 mg/kg BW, divided into two doses given 24 h apart, in addition to fluid therapy (multiple electrolyte solution). Despite this treatment, only slight improvement was observed. The urine became straw-coloured and all dogs regained their appetite and desire to drink, but the neurological symptoms persisted. Therefore magnetic resonance imaging was performed, under general anaesthesia induced by infusion of propofol at 2 mg/kg, following premedication with atropine (0.05 mg/kg s.c.) and medetomidine (0.1 mg/kg i.m.). Following intubation the dogs were placed in in low-field magnetic resonance (0.25 Tesla) in sternal recumbency.

The MRI showed ischaemic changes in all eight dogs – in the cerebellar lobe (n=3), frontal lobe (n=3) and midbrain (n=2).

All dogs were treated with prednisone (0.5 mg/kg/day per os) and primidone (20 mg/kg). Four of the dogs additionally received BrainActiv Balance (Vetfood) in the amount of 1 capsule/10 kg BW for three months.

As a result of the treatment the dogs' condition began to stabilize. Within a few days the strabismus and opisthotonos resolved. Sporadic seizures and impairment of consciousness persisted longer, resolving on average after 29 days in the group of dogs receiving BrainActiv Balance and after 42 days in the group that did not receive the supplement. Administration of the supplement was not found to induce any

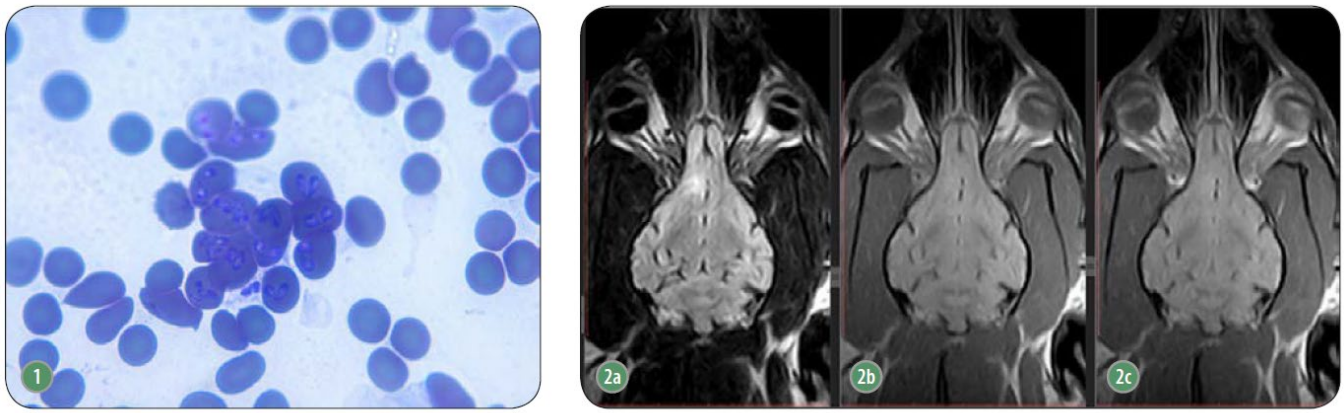

Figure 1. Blood smear stained by the Diff-Quick method. Merozoites of Babesia canis present within the erythrocytes of a dog.

Figure 2. a, b, c. Ischaemic change in the course of cerebral babesiosis. MRI of the encephalon showed a poorly delimited lesion in the rostral region of the right frontal lobe in contact with the median fissure of the brain with high signal intensity on the T2-weighted and FLAIR sequences (Fig. 2a). The change is isointense on the T1-weighted sequence (Fig. 2b) and the T1-weighted sequence following administration of the contrast agent (Fig. 2c). No signal amplification was shown.

side effects, such as vomiting or diarrhoea. The results of biochemical analysis of the serum of all four dogs receiving the preparation remained within physiologically normal ranges throughout the period of administration.

Discussion

Cases of the cerebral form of babesiosis are increasingly noted in dogs. It presents as ataxia, paralysis, seizures, uneven pupil dilation, nystagmus, temporary loss of consciousness, aggression, and vocalization, and may result in death (21).

Cerebral babesiosis is suspected when a dog shows nervous symptoms, Babesia infection is diagnosed, concomitant infections have been ruled out, and in case of the animal's death, the presence of protozoa in the brain has been confirmed by histopathological or molecular tests (17,21).

The main cause of this form of the disease is the development of inflammation and impaired blood flow in the vessels of the brain. Other causes of cerebral babesiosis are hypoxia, hypoglycaemia, metabolic disorders, and impairment of neurotransmission induced by nitric oxide (17).

Impaired blood flow is caused by the release of soluble parasitic antigen (SPA) in the host by Babesia, leading to activation of the kallikrein system, which converts kininogen to kinins. Kinins dilate the blood vessels, resulting in a decrease in blood pressure. Erythrocytes infected with protozoa directly or indirectly intensify the acute phase response and activate the clotting system. These effects lead to an increase in the concentration of fibrin, which coats both healthy erythrocytes and those infected with parasites. This increases their stickiness and tendency to agglutinate. The entire cascade of these processes impairs blood flow through small vessels, which indirectly contributes to an increase in parasitaemia. The breakdown of erythrocytes increases the release of phospholipids from the cell membrane. Phospholipids initiate a cascade of transformations beginning with activation of clotting factor X and conversion of prothrombin to thrombin, which in turn stimulates the conversion of fibrinogen to fibrin. All of these processes induce the development of disseminated intravascular coagulation (DIC) (23,24), which may result in dysfunction of the internal organs, especially the kidneys, liver, lungs and brain (25).

Apart from blood stagnation, another factor contributing to impairment of blood flow is erythrocyte sequestration. This phenomenon involves accumulation of infected erythrocytes and their adhesion to the vascular endothelium. This is made possible by special interactions between these two structures. The entire sequestration mechanism is suspected to be similar to that observed in malaria in humans. Infected erythrocytes act on the endothelium on a receptor-ligand basis. RBCs infected with parasites enhance the inflammatory response mechanism and increase levels of inflammatory cytokines IL-1, IL-6 and TNFα (26). Inflammatory reactions increase adhesion of blood cells to the endothelium, which contributes to blood flow impairment in the microcirculation. This results in a rise in blood pressure, the development of local inflammation, and thus blood vessel dilation and an increase in parasitaemia (21).

In all eight dogs included in the observations, neurological symptoms were likely caused by brain tissue hypoxia, which was confirmed by magnetic resonance imaging. Appropriate causal and symptomatic treatment resulted in the animals' recovery.

The recovery time of the dogs receiving the BrainActiv Balance supplement was much shorter than in the animals that did not receive it, which indicates that it can accelerate the recovery of patients with cerebral babesiosis. Indications for administration of BrainActiv Balance are impaired concentration and consciousness in animals. Its main ingredients are fatty acids (omega 3), vitamin C, vitamin E, N-acetyl-L-cysteine, and L-carnitine. This composition helps to improve brain function, impaired not only by ageing processes, but also as a result of injuries and strokes.

Researchers at Columbia University Medical Center in New York conducted a study on 10-day-old mice with cerebral hypoxia-ischaemia resulting in stroke-like damage. The rodents were administered DHA or EPA (which are also ingredients in BrainActiv Balance). Brain functions were tested 24 hours after hypoxia and then again after 8 and 9 weeks. In the mice receiving DHA, brain damage after 24 hours was much smaller than in the mice from the control group. Similar results were noted in the subsequent tests. The researchers detected increased DHA concentrations in the mitochondria, which may have been damaged by free radicals following stroke. These results suggest that administration of DHA following stroke or a similar episode may protect the mitochondria against the harmful effects of free radicals (27). It seems likely that this took place in the patients observed in the present study.

The results of research by Heinemann and Bauer (28) indicate that administration of DHA to pregnant dogs improves nervous system development in puppies and the learning process in young dogs. A similar function is attributed to L-carnitine. This natural, vitamin-like substance present in the cells of the body is synthesized from lysine and methionine in the liver, kidneys and brain. L-carnitine performs an important role in lipid metabolism. It transports long-chain fatty acids to the mitochondria, where they are oxidized and the energy needed for cell functioning is produced. L-carnitine regulates the amount of acyl-CoA and CoA in the cytosol and mitochondria. It is a donor of acetyl groups in biosynthesis of acetylcholine. Its other functions include removal of excess acyl-CoA from the mitochondria, involvement in oxidation of very-long-chain fatty acids in the peroxisomes, and antioxidant activity. Clinical studies have shown that L-carnitine has a beneficial effect on the nervous system (29,30,31). In human medicine, long-term administration of L-carnitine to young people with intellectual disabilities improves their learning ability and reflexes. Administration to patients with Alzheimer's disease improves memory and has a beneficial effect in depressive states (32).

The other ingredients of BrainActiv Balance primarily exhibit antioxidant effects, protecting the nervous system against the harmful effects of reactive oxygen species (ROS). N-acetyl-L-cysteine prevents apoptosis and cell damage caused by ROS. It is a precursor of glutathione, which is one of the most important antioxidants. Administration of N-acetyl-L-cysteine in combination with vitamins A, E and C and saturated fatty acids significantly reduces the level of ROS in the body, thereby protecting nerve cells from damage (33).

Analysis of the composition of BrainActiv Balance and the literature data in conjunction with our own observations suggests that although

our observations were conducted on a small group of dogs with the cerebral form of babesiosis, the use of this type of preparation in patients appears to significantly reduce the convalescence period and accelerate the animals' recovery. Importantly, the composition of the supplement was designed in such a way that it can also be used successfully in other brain diseases resulting from the effects of free radicals on brain tissue.

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Author's address: prof. dr hab. Łukasz Adaszek, Klinika Chorób Zakaźnych, Wydział Medycyny Weterynaryjnej UP w Lublinie, ul Głęboka 30, 20-612 Lublin, e-mail: ukaszek0@wp.pl.