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Review Article

BABESIOSIS: A MAJOR THREAT TO CANINE POPULATION

GUPTA K.K.[1]*, KAUR J.[1], PUNIA S.[1], GUPTA N.[2] AND SINGH G.[3]

[1]Department of Veterinary Medicine, College of Veterinary Science, Rampura Phul, 151103, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, 141012, Punjab, India

[2]Animal Health Complex, ICAR- National Dairy Research Institute, Karnal, 132001, Haryana, India

[3]Department of Veterinary Clinical Complex, College of Veterinary Science, Rampura Phul, 151103, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, 141012, Punjab, India

*Corresponding Author: Email - dr.kapil09@gmail.com

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Abstract: Babesiosis is a common problem in canine population causes frustration among pet owner and veterinarians. It is a tick born hemoprotozoan disease affecting vast variety of canine breed of almost all age group. Life cycle include only intraerythrocytic stage known as merozoite which are basically daughter parasite. Clinical signs consist of high-grade fever, anaemia, jaundice, haemoglobinuria etc. Diagnosis by conventional method is most common in practice although serological and molecular diagnosis can also be available especially for carrier animals and for subclinical disease. Therapeutic management include drug and drug combinations with positive outcome. Common drugs used as a first line of treatment are Diminazene aceturate and Imidocarb dipropionate although different combination of drugs like atovaquone and azithromycin, buparvaquone and azithromycin or clindamycin (CLDM), metronidazole (MNZ) and doxycycline has been successfully used against canine babesiosis. Supportive therapy includes blood transfusion, fluid and electrolyte therapy, corticosteroids and immunomodulators. Control of tick population, vaccination, safe blood transfusion, avoiding dog fitting are key to control the babesiosis in canine population.

Keywords: *Babesia, Diminazene, blood transfusion, Imidocarb*

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Introduction

Canine babesiosis is a tick-borne, hemoprotozoan disease characterized by varying degrees of haemolytic anaemia, splenomegaly, thrombocytopenia and fever.

Etiology

Disease is caused by apicomplexan parasites of the genus Babesia which has been reported worldwide including India [1]. Babesia organisms are frequently classified as large or small. The large Babesia spp. (measuring between 3 and 5 µm) previously considered to be *B. canis*, currently include *B. canis*, *Babesia rossi* and *Babesia vogeli* as distinct species [2] while small Babesia species (measuring 1-3 µm) include *B. gibsoni*, *Babesia conradae* and the recently reported "Babesia vulpes" [3]. Members of the genus Babesia readily parasitize red blood cells resulting into progressive anemia. The severity of the disease is determined by various factors like type of Babesia species associated with disease, age and the immune status of the host. Main vectors for Babesia species are hard ticks within which it undergoes the sexual conjugation and the sporogony. A blood meal will ultimately transmit the sporozoites from salivary gland of the tick to the new vertebrate host, whereupon the protozoan life-cycle is completed by asexual replication (merogony) within the erythrocyte, where the parasites appear as merozoites.

Epidemiology

Presences of competent ticks determine the geographical distribution of Babesia spp. *B. rossi* is the most virulent species and occurs predominantly in southern Africa. *B. vogeli* is the least pathogenic species occurring in France, Australia, Japan, Brazil, South Africa and the USA and usually causes mild disease in adult dogs but severe disease in some puppies [4]. In India both *B. canis* and *B. gibsoni* are prevalent, and almost all states of the country are affected.

Clinical Manifestations

Major clinical signs associated with canine babesiosis are apathy, weakness, anorexia, pale mucous membranes and a poor general condition. Haematological abnormalities include anaemia (regenerative or non-regenerative) and thrombocytopenia. Other abnormalities that can be detected include hypoalbuminemia and hyper-bilirubinemia [5].

Diagnosis

Blood smear examination for parasite visualization

Morphological identification of parasite by Giemsa or Wright's-stained blood smears in host's erythrocyte is the simplest and most accessible diagnostic test for most veterinarians with good sensitivity especially during acute phase of disease. Microscopic evaluation of piroplasmic state is still the only viable available option for detection of disease in endemic area. Chances of the positive microscopic result will enhance by adopting proper sampling techniques. Light microscopy is very important to detect large form of Babesia (e.g., *B. canis*) but small piroplasms (*B. gibsoni*, *B. microti*-like sp.) are hard to observe by light microscopy, which has a relatively low sensitivity [6]. Moreover, in case of chronic infection or carrier stage parasitaemia is oftenly very low or intermittent hence the identification of piroplasms remains a significant challenge. Sometimes infection may be chronic or due to less virulent species such as *B. canis* and *B. vogeli* causing the parasitaemia below the microscopic detection limit making the diagnosis more problematic in thin blood smear. In such cases thick smears (not alcohol fixed) may be helpful in detecting the parasite.

Haematology

The major haematological alterations include normocytic and normochromic anaemia, Leukocytosis with either normal to subnormal neutrophil counts and thrombocytopenia (severe in the acute phase of infection) [7]. Main biochemical changes are elevation of hepatic enzymes like ALP, ALT and AST, low total serum protein and albumin level. Serum bilirubin concentration becomes elevated due to hepatopathy and hemolysis. In advance cases with nephropathy, there will be proportionate increase in serum urea and creatinine levels because of decreased renal perfusion, as a result of hypovolaemia, decreased blood pressure and decreased myocardial function secondary to anemia. Some reports evident elevation of acute phase protein (α1-acid glycoprotein) in dogs with *B. rossi* infection, but levels do not correlate with severity of disease or outcome [8].

Electrocardiogram (ECG findings)

ECG examination reveals presence of varying degree of arrhythmias like sinus arrest, sinoatrial block, first- and second-degree atrioventricular block, ventricular tachycardia and ventricular premature depolarizations. ECG abnormalities include prolonged QRS interval, low amplitude and notching of R waves, ST segment deviation and large T waves [9].

Urinalysis

A recent study revealed presence of both glomerular and tubular dysfunction during Babesia infection as suggested by high concentrations of urinary IgG, urinary CRP and urinary RBP. Routine urine test may reveal presence of bilirubinuria, haemoglobinuria and proteinuria [10]. Urinary enzymatic activity of GGT and ALP becomes altered but upto minimum level which is difficult to detect thus limiting their use as diagnostic tests [11].

Serology

Common serological tests applied for diagnosis of babesiosis are indirect immunofluorescence (IFAT) and enzyme-linked immunosorbent assay (ELISA). One of the advantages of IFAT or ELISA is that these tests allow us to determine the antibody levels and therefore establish whether they are high or low and also used for early and specific detection of acute infections. These serological techniques are of limited use because of non-establishment of specificity and sensitivity [5].

Molecular diagnosis

Molecular techniques are used for differentiation of parasite at species level and thus provide valuable informations regarding disease prognosis. Various molecular techniques, used for this purpose are semi-nested PCR [12] reverse line blotting [13] and PCR-restriction fragment length polymorphism analysis [14]. These techniques (especially PCR) more reliable for the identification of the etiological agents compared to direct detection by light microscopy or serology. PCR is more sensitive and provides evidence of an active and ongoing infection in a clinical setting.

Imaging techniques

Most common diagnostic imaging technique used for the detection of babesiosis is ultrasonography. Hepatomegaly and splenomegaly with diffuse, hypoechoic, heterogeneity and diffuse homogenous increased in renal cortical echogenicity and increased corticomedullary definition are some consistent findings on abdominal ultrasonography in dogs infected with *B. canis* [15]. Dogs infected with *B. rossi* and *B. canis* having gastrointestinal signs and abdominal pain is reported to have ultrasonographic changes in the pancreases [16] which are found to be consistent with acute pancreatitis and included duodenal atony and peripancreatic fat hyperechogenicity.

Differential diagnosis

Disease should be differentiated from other causes of haemolytic anaemia such as haemobartonellosis, autoimmune haemolytic anaemia, pyruvate kinase deficiency and Heinz body haemolytic anaemia. Other differentials include immune-mediated thrombocytopenia, systemic lupus erythematosus, leptospirosis, rickettsial diseases, dirofilariasis with caval syndrome, zinc toxicity and neoplasia.

Therapeutic management

Imidocarb dipropionate is used at the dose rate of 6.6 mg/kg either by intramuscular or subcutaneous route. Many reports have been proposed regarding mechanism of action of Imidocarb and include Inhibition of the inositol entry into parasitized erythrocytes, resulting in starvation of the parasite [17] or binding with and damage to the nucleic acid of parasite and inhibition of cellular repair and replication [18]. The most common adverse effects associated with Imidocarb include pain at injection site, salivation, drooling and nasal drip or vomiting. Premedication with atropine @ 0.05 mg/kg body weight can prevent these adverse effects. Diminazene aceturate is widely used in tropical countries for the treatment of *Babesia gibsoni* infection of dogs. It is used at the dose rate of 3.5 mg/kg body weight by deep intramuscular injection. Relapse in case of *B. gibsoni* infection is common with diminazene aceturate as it often fails to eliminate parasite from affected dogs. Diminazene has narrow margin of safety and can induce fatal nervous complications after 1-2 days of overdose. Clinical signs of diminazene toxicity include depression or stupor, continuous vocalisation, ataxia, opisthotonos, extensor rigidity, nystagmus and seizures [19].

Atovaquone and azithromycin combination has been shown to first effective treatment against *B. gibsoni* infection. [20]. Combined use of atovaquone and azithromycin produces an additive or synergistic effect, while the single use of each drug tends to result in a relapse of clinical signs. Mechanism of action of atovaquone involves blocking of mitochondrial electron transport causing inhibition of pyrimidine and ATP synthesis [18]. Azithromycin inhibits translation of mRNA and bacterial protein synthesis by binding to the 50S subunit of the prokaryote ribosome. It exerts its antiprotozoal effects by specific action on apicoplast, non-photosynthetic plastid organelles found in apicomplexans parasites [21]. Combination therapy of clindamycin (CLDM), metronidazole (MNZ) and doxycycline (DOXY) is an effective therapeutic strategy for *B. gibsoni* infection [22]. However, duration of treatment is very long in order to achieve good therapeutic effect [23]. Other drugs used to treat babesiosis in dogs include quinuronium sulfate, trypan blue solution and pentamidine; experimental treatments include artesunate, plant extracts or tick peptides [24].

Supportive treatment

Fluid therapy

It is indicted in the patient with history of renal disease, old age, shock, haemoglobinuria and in patient showing clinically significant dehydration. Amount of replacement fluid to be given is determined by extent of dehydration as per given schedule-

Mildly dehydrated (approximately 5%) - 50ml/kg body weight
Moderately dehydrated (approximately 10%) - 100 ml/kg body weight
Severely dehydrated (15%)- 150 ml/kg body weight

Main purpose of fluid administration is to restore blood volume, correction of electrolyte and acid base imbalance, maintenance of sufficient diuresis and prevention of red blood cell sludging in capillaries [25]. Most common types of fluids are isotonic crystalloid (0.9% normal saline), hypotonic crystalloid (Ringer's lactate) or colloidal solutions (Hetastarch@10 to 20 ml/kg). During fluid administration close monitoring of respiration and pulmonary sound should be properly accessed.

Whole blood/ RBC/plasma transfusion

It is indicated for the correction of anemia and should be done if haematocrit value becomes ≤15% and clinical signs such as dyspnoea or tachypnea are evident. Since degree of parasitaemia is not strongly related with degree of anaemia, it is not recommended to estimate degree of parasitaemia before blood or its component transfusion. Preferred fluid for treating haemolytic anaemia is packed erythrocytes which can be administered at the dose rate of 20mL/kg proper history regarding any previous blood transfusion is mandatory because cross matching depend upon the fact whether dog has previously been transfused or not.

Since dogs do not have naturally occurring alloantibodies cross matching is not mandatory for the first transfusion but it must be performed if it is doing for 2nd time onwards. Initial rate of blood transfusion should be 2ml/ kg/hr for first 30-60. During blood transfusion carefully observe the dog for any transfusion reactions, such as a sudden rise in body temperature and/or respiratory rate and lip and ear pinna swelling etc.

Immunosuppressants

Most commonly used drug for imunosuppression is prednisolone (@2 mg/kg/day) which is recommended if the dog has moderate-to-severe clinical signs (sudden collapse or spontaneous bleeding) associated with immune-mediated haemolytic anaemia (Positive Coomb's or antinuclear antibody tests) or immune-mediated thrombocytopenia (Platelets count- 20,000and 40,000/ µl) [26].

Other supportive therapies

Other supportive therapies depend on the clinical signs and/or laboratory abnormalities, for example, oxygen therapy should be used when there is respiratory distress and antiemetics to counter vomiting. If the dog is stable and does not require hospitalization, then treatment should be restricted to antiprotozoal agents [27].

Prevention and control

The most effective way to prevent the infection is regular control of the tick vectors. It can be achieved by routine dipping or spraying of dog, using tick collars, application of readymade spot-on preparations. Since the transmission of Babesia takes minimum 48 hours, regular examination of dogs for the presence of any ticks and to remove it soon after they attach is important. Since blood transfusion increases the risk of transmission of merozoites from donor to recipient circulation, proper screening of donor dog for babesiosis, preferably by polymerase chain reaction, is mandatory. It has also been reported that *B. gibsoni* can be transmitted by transfer of blood via local wound formed during dog fighting. So, if the owner is having more than one pet and one of them is affected with babesiosis, they should take care of dog not to fight among themselves. Vaccine against *B. canis* is available in Europe with a reported efficacy of 70-100% [28]. Recently a bivalent vaccine derived from soluble parasite antigens from *B. canis* and *B. rossi* named as Pirodog® (Merial). It has been shown to reduce duration and severity of clinical signs [29]. Although vaccination against canine babesiosis does not play any role in prevention of infection, it does seem to block the initiation of pathologic processes involved in the pathogenesis of the disease [30]. Age of first vaccination is five month and should be annually re-administered. It does not provide cross immunity against other Babesia species like *B. gibsoni*. Vaccines against other Babesia species such as *B. gibsoni* are currently being developed including recombinant antigen and DNA vaccines.

Conclusion

Canine babesiosis is one of the most common tick born hemoprotozoan disease affecting canine population all over the world. It is a leading cause of canine mortality and frustration to animal owner. Earlier diagnosis and treatment of disease is the only way to save the animal because once systemic infection occurs there is multiorgan involvement leading to poor prognosis. Subclinical cases should be diagnosed earlier with the help of different serological and molecular tests in order to prevent the development of clinical form of disease. Therapeutic management of canine babesiosis should be done by using various antiprotozoal drugs and drug combination like diminazene aceturate, Imidocarb dipropionate and combination of Atovaquone and azithromycin, Buparvaquone and azithromycin or clindamycin (CLDM), metronidazole (MNZ) and doxycycline (DOXY) combination. Supportive therapy includes various crystalloids and colloid solution, use of corticosteroid and many immunosuppressive drugs. Although not even a single drug or drug combination is efficient to completely eliminate the parasite from blood of host, treated animal will most of the time act as carrier and may spread infection to other animals. Prevention of tick exposure, timely vaccination and safe blood transfusion are some of the important measures to save the animal from this fatal infection.

Application of research: Study of pathophysiology of Babesiosis may assist in diagnosis and better therapeutic management of disease.

Research Category: Veterinary Medicine

Abbreviations:

DOXY-Doxycycline, PCR-Polymerase chain reaction, ECG-Electrocardiogram, ALP-Alkaline phosphatase, ALT-Alanine transaminase,
AST-Aspartate transaminase, MNZ-Metronidazole, CLDM-Clindamycin

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****Principal Investigator or Chairperson of research: Dr K.K. Gupta**
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