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Dogs Naturally Infected with *Hepatozoon* spp. in the Sertão Paraibano Mesoregion, Brazilian Semiarid

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ABSTRACT

***Background*:** Canine hepatozoonosis is a disease caused by protozoa of the genus *Hepatozoon*. It is transmitted when dogs ingest infected ticks and via the vertical route. In Brazil, it is often considered to be a subclinical disease, but it is still unclear whether more severe clinical signs develop in young, elderly or debilitating animals. The aim of this study was to report 82 cases of dogs naturally infected with *Hepatozoon* spp. in the Sertão mesoregion of Paraíba, in order to characterize the clinical signs, haematological findings, presence of concomitant diseases and epidemiological aspects.
***Cases*:** Records of 82 dogs that tested positive for *Hepatozoon* spp. in direct blood smears were studied. These animals were treated at the Veterinary Hospital of the Federal University of Campina Grande, located in the municipality of Patos, Paraíba, Brazil. The following data were obtained from each animal's clinical record: age, sex, breed, presence of tick infestation, clinical signs and blood count data. According to the clinical findings, the animals were divided into 4 groups: 1- animals with co-infections; 2- with severe or debilitating conditions; 3- with non-specific clinical signs, and 4- asymptomatic. The most affected dogs were puppies up to 6 months old ($P = 0.0002$) and mixed breed ($P = 0.0014$). Infection was found in three puppies up to 30 days old. There was a high frequency of animals that presented ticks at the time of the clinical examination ($P = 0.0006$). Of the 82 positive dogs, 49 had severe or debilitating illnesses and were the most affected group ($P < 0.001$), 20 had non-specific clinical signs, 10 had co-infections with other agents and 3 were asymptomatic. The main conditions observed were trauma, neoplasms, co-infections with other haemoparasites and gastroenteritis. Anaemia and thrombocytopenia were the main haematological alterations, which were observed even in asymptomatic animals.
***Discussion*:** This is the 1st study to show that canine hepatozoonosis is present in the Sertão mesoregion of Paraíba, Northeast region of Brazil and to evaluate epidemiological aspects associated with the infection. The infection found in puppies suggests vertical infection. Diagnosis in this age group is extremely important, because in puppies the disease may present in an acute form, producing more severe clinical signs, due to the fact that immunity is not fully developed in these animals. Mixed breed dogs were more affected, which may be related to the fact that these animals belong to families with fewer socio-economic resources when compared to the owners of pedigree dogs, directly influencing basic care for the animal. Tick infestation was the main predisposing factor and highlights the need for owners to control ectoparasites. In most of the dogs the *Hepatozoon* spp. infection was not the main cause, presenting itself as a secondary laboratory finding. It is therefore possible that these associated diseases have reduced the resistance of the host's immune system to *Hepatozoon* spp. There were also animals that presented only non-specific clinical signs that correlate with the pathogenesis of the parasite. Anaemia and thrombocytopenia were the main haematological alterations observed and proved to be indicative of *Hepatozoon* spp. infection, especially in subclinical cases. It is suggested that veterinary clinicians should request that blood smears be tested for *Hepatozoon* spp. in dogs with debilitating diseases, non-specific clinical signs or haematological disorders.

Keywords: canine hepatozoonosis, haemoparasites, anaemia, thrombocytopenia, vertical infection.

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INTRODUCTION

Canine hepatozoonosis is a disease caused by protozoa of the genus *Hepatozoon*, and transmission in dogs occurs through the ingestion of infected ticks [17] and via vertical route [15]. In infected dogs, gamonts parasitising neutrophils may be seen in blood smears, bone marrow and lymph nodes [16] and meronts may be found in the spleen, liver, kidneys [12], lungs, pancreas and pleura [4]. This large number of parasitised organs may result in a wide variety of clinical signs, making the disease difficult to be clinically diagnosed.

It is often deemed as a subclinical disease [9], but it is still unclear whether more severe clinical signs develop in young, elderly or debilitated animals. In addition, the disease is immunosuppressive [10], making infected animals more susceptible to secondary infections.

Research into this parasite has therefore intensified, mainly with the aim of elucidating the prevalence, pathogenicity and epidemiology of the disease in dogs in Brazil. The aim of this study was to report 82 cases of dogs naturally infected with *Hepatozoon* spp. in the Sertão mesoregion of Paraíba, Northeast region of Brazil, in order to characterize the clinical signs, haematological findings, presence of concomitant diseases and epidemiological aspects.

CASES

Records of 82 dogs that tested positive for *Hepatozoon* spp. in direct blood smears were studied. The data was gathered between January 2016 and July 2017 at the Veterinary Hospital of the Federal University of Campina Grande (UFCG) located in the municipality of Patos, Paraíba state, in the Northeast region of Brazil.

The diagnosis was made by direct research on blood smears prepared and stained using the rapid panoptic method. The following data from each animal's clinical file were observed: age, sex, breed, presence of tick infestation, clinical signs and blood count data.

According to the clinical findings, the animals were divided into 4 groups:

1. Animals with co-infections: Animals that also tested positive for other infections. Diagnosis was carried out by direct haemoparasite testing on blood smears to identify *Ehrlichia* spp., *Babesia* spp., Lentz's corpuscle and *Leishmania* spp. using the S7® ELISA kit[1].
2. Animals with severe or debilitating conditions: Animals that have suffered severe trauma, have neoplasms confirmed by biopsy and/or cytology, gastroenteritis, nervous signs, pyometra, severe bleeding disorders or heart disease.
3. Animals with non-specific clinical signs: Animals that had no obvious associated diseases, only non-specific clinical signs.
4. Asymptomatic animals: Animals with no clinical signs that have undergone elective examinations.

To compare the proportions between the categories of the variables gender, age, breed, tick infestation and clinical profile, the adherence chi-square test with 5% ($P \leq 0.05$) significance was used, and the analyses were carried out using the BioEstat 5.3 statistical software.

In the 82 dogs studied, *Hepatozoon* spp. gametocytes were visualised exclusively inside neutrophils (Figure 1). Of these animals, 44 were females and 38 males (Table 1). After statistical analysis, it was found that there was no significant difference between the 2 categories ($P = 0.581$). Regarding the age, 30 (37%) of the animals were puppies up to 6 months old, which was the main age group affected ($P = 0.0002$). Fifty-six (68%) animals were mixed breed and 26 (32%) were of a defined breed (Poodle, Pinscher, Duchshund, Pekingese, Labrador, Cocker Spaniel or Dalmatian). Statistical analysis showed that mixed breed dogs were more affected than dogs with a defined breed ($P = 0.0014$). It was also found that 57 (69%) of the animals presented ticks at the time of the clinical examination ($P = 0.0006$).

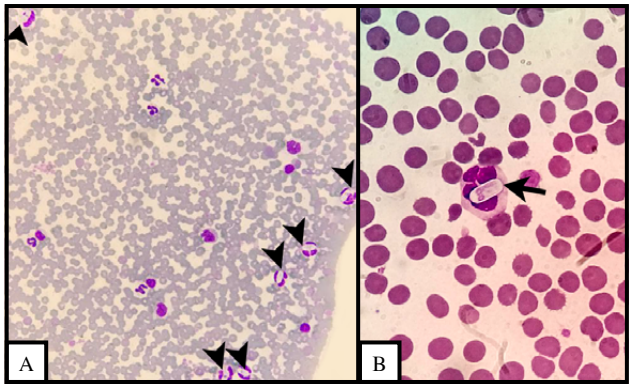

Figure 1. A- Photomicrograph of gamonts of *Hepatozoon* spp. infecting neutrophils (arrowhead) in a dog with severe parasitemia [400x]. B- Photomicrograph of *Hepatozoon* spp. infecting neutrophil (arrow) in a dog [1000x].

Table 1. Epidemiological profile of 82 dogs naturally infected with Hepatozoon spp. in the Sertão Paraibano mesoregion, Brazil, from January 2016 to July 2017.

Variables	Categories	Dogs (n)	Frequency (%)	*P*-value
Sex	Female	44	54	0.581
	Male	38	46	
Age	≤ 6 months	30	37	0.0002
	6 months - 1 year	10	12	
	1 - 2 years	10	12	
	3 - 5 years	13	16	
	6 - 9 years	11	13	
	≥ 10 years	8	10	
Breed	Mixed breed	56	68	0.0014
	Purebreed	26	32	
Tick infestation	Yes	57	69	0.0006
	No	3	4	
	Not informed	22	27	

n: number of animals.

Clinically, 10 (12%) dogs were confirmed to have co-infections with other agents, 49 (60%) with severe or debilitating conditions, 20 (24%) with non-specific clinical signs and three (4%) were asymptomatic (Table 2). Statistical analysis showed that animals with severe or debilitating conditions were the most affected ($P < 0.001$). As for the 10 animals with co-infections, 4 were also infected with *Babesia* spp., 3 with *Ehrlichia* spp., 2 with *Leishmania* spp. and in one animal corpuscle of Lentz was observed. As for the animals with serious or debilitating conditions, 15 had suffered serious trauma, 11 had neoplasms, 8 gastroenteritis, 6 nervous signs, 5 pyometra, 2 serious bleeding disorders and 2 had heart disease. It is worth noting that there were no cases associated with ophthalmic, dermatological, endocrine-metabolic, urinary or poisoning complaints.

In the anamnesis, it was noted that most of the dogs that suffered serious trauma did not receive immediate veterinary clinical care after the injury, but were taken to the Veterinary Hospital around a month after the trauma. Some of these animals had open fractures and paresis of the hind limbs, as well as apathy and anorexia. Severe clinical conditions were also observed in bitches with pyometra. As for neoplasms, the most prevalent were transmissible venereal tumours and mammary neoplasms.

As for the 20 animals that showed non-specific clinical signs, the main ones commonly observed were apathy, lymphadenopathy, anorexia, hypochromic mucous membranes, dehydration, weight loss and inappetence (Table 3).

Regarding the haematological alterations, 76% of the animals showed anaemia and 57%

Table 2. Clinical profile of 82 dogs naturally infected with *Hepatozoon* spp. in the Sertão Paraibano mesoregion, Brazil, from January 2016 to July 2017.

Clinical profile	Dogs (n)	Frequency (%)	*P*-value
Co-infections *	10	12	< 0.001
Severe or debilitating conditions **	49	60	
Non-specific clinical signs	20	24	
Asymptomatic	3	4	

n: number of animals. **Babesia* spp., *Ehrlichia* spp., *Leishmania* spp. and corpuscle of Lentz. **Traumas, neoplasms, gastroenteritis, nervous signs, pyometra, severe bleeding disorders and heart disease.

Table 3. Main clinical signs presented by 20 dogs from the Sertão Paraibano, Bazil, naturally infected with *Hepatozoon* spp. and who had no other obvious concomitant disease, from January 2016 to July 2017.

Clinical signs	Dogs (n)	Frequency (%)
Apathy	9	45
Lymphadenopathy	9	45
Anorexia	8	40
Hypocoloured mucosa membranes	7	35
Dehydration	6	30
Weight loss	5	25
Inappetence	4	20
Vomiting	3	15
Coughing	3	15
Diarrhoea	1	5

n: number of animals.

thrombocytopenia (Table 4). Normochromic normocytic anaemia was the most common (50%), especially in animals with severe or debilitating conditions. Mild to moderate anaemia was the most common (62%), whilst leukocyte disorders and hypoproteinemia were less common. In addition, haematological alterations were observed in 2 of the 3 asymptomatic animals that were treated for elective surgery: 1 had anaemia and the other thrombocytopenia.

DISCUSSION

In this study, the most affected age group was puppies up to 6-months-old, 3 of which were up to 30-days-old. Considering the parasite's biological cycle, this result suggests vertical infection, since in vertically infected dogs, gamonts in neutrophils in the peripheral blood can already be found around 16 to 60 days after birth [15], whilst in dogs infected by ingesting ticks, gamonts are usually seen around 28-43 days post-infection [3]. In view of this, it is unlikely that 1 or 2-day-old neonates would have ingested the infected tick and a diagnosis could be made through direct research in 1-month-old animals. Hepatozoonosis in dogs is considered to be a low pathogenicity disease with a subclinical character [2], but in puppies, due to the fact that immunity is not fully developed, it may present in an acute form, producing more severe clinical signs.

Mixed breed dogs were more frequent among those infected, which may be related to the fact that most of the time these animals belong to families with fewer socio-economic resources when compared to owners of pedigree dogs. It's worth emphasising that the owner's financial status has a direct influence on basic animal care and consequently on susceptibility to diseases. In addition, the high frequency of animals with tick infestation among those infected highlights the importance of the guidelines given to owners to carry out ectoparasite control on their pets, since this is the main predisposing factor for the occurrence of the disease, as dogs acquire canine hepatozoonosis after ingesting infected ticks [17].

In most of the animals studied, infection with *Hepatozoon* spp. was not considered the main cause, but a secondary laboratory finding, as 72% of the dogs had concomitant diseases, some of which were acute and severe (co-infections, gastroenteritis, pyometra, nervous signs and severe haemorrhagic disorders) and other debilitating (trauma, neoplasms and heart disease). It is possible that these associated diseases have reduced the resistance of the host's immune system to *Hepatozoon* spp., leading to an increase in parasitaemia to levels detectable during blood smear research.

In the literature, cases of hepatozoonosis associated with co-infections with other haemoparasites have already been reported [6,14,21]. However, it is worth highlighting that this is the first study to show *Hepatozoon* spp. infection associated with severe trauma, neoplasms and pyometra. The fact that there were no cases associated with ophthalmic, dermatological, endocrine-metabolic, urinary or poisoning complaints may be related to the fact that these conditions may

Table 4. Haematological alterations in 82 dogs naturally infected with *Hepatozoon* spp. in the Sertão Paraibano mesoregion, Brazil, from January 2016 to July 2017.

Haematological alterations	Co-infections (n=10)	Severe/debilitating conditions (n=49)	Non-specific clinical signs (n=20)	Asymptomatic (n=3)	Total (%)
Anaemia	10 (100%)	39 (80%)	12 (60%)	1 (33%)	62 (76%)
Normochromic normocytic	5	27	8	1	41 (50%)
Hypochromic normocytic	2	7	1	0	10 (12%)
Normochromic microcytic	2	3	2	0	7 (8%)
Hypochromic microcytic	0	2	0	0	2 (2%)
Hypochromic macrocytic	1	0	1	0	2 (2%)
Level (Anaemia)					
Mild	4	16	3	1	24 (29%)
Moderate	4	18	5	0	27 (33%)
Severe	1	4	4	0	9 (11%)
Very severe	1	1	1	0	3 (4%)
Leucocytosis with neutrophilia	1	13	4	0	18 (22%)
Leucocytosis with lymphocytosis	1	2	0	0	3 (4%)
Leucopenia with neutropenia	2	4	1	0	7 (8%)
Leucopenia with lymphopenia	1	5	2	0	8 (10%)
Lymphopenia	2	5	4	0	11 (13%)
Thrombocytopenia	5	27	14	1	47 (57%)
Hypoproteinaemia	3	6	5	0	14 (17%)

n: number of animals.

not lead to conditions as debilitating as those observed in this study.

It is worth noting that 20% of the animals showed non-specific clinical signs, corroborating the findings of other studies with dogs infected with *Hepatozoon* spp. in Brazil [1,7,8,19]. All the clinical signs observed in this group correlate with the pathogenesis of the parasite, since this protozoan causes lesions in various organs [4]. The non-specificity and variability of the clinical signs presented by infected dogs show that the disease is difficult to diagnose clinically and is debilitating.

Anaemia and thrombocytopenia were the main haematological changes observed, and anaemia has already been reported in other studies in dogs with hepatozoonosis [1,5,18,19]. In general, anaemia and thrombocytopenia are non-specific haematological alterations, as they can be found in various diseases due to antigenic stimulation and adherence of immune complexes that stimulate phagocytosis of healthy cells and consequently a decrease in these cell types in the

circulatory system [22]. However, the fact that 2 of the 3 asymptomatic animals also had haematological disorders shows that anaemia and thrombocytopenia can be indicative of *Hepatozoon* spp. infection, especially in subclinical cases.

It should be noted that commercial serological tests for the *Hepatozoon* spp. diagnosis have not yet been developed, and it is commonly diagnosed through the visualisation of gametocytes in blood smears. Another option would be to use molecular techniques, as they are highly sensitive and may differentiate between species [11,13,20]. However, in the laboratory routine, research on blood smears is still the best option because it is a quick technique with high specificity for the genus and low cost. Therefore, it is important for veterinary clinicians to request *Hepatozoon* spp. testing on blood smears of dogs with debilitating diseases, as well as in cases where the animals show non-specific clinical signs and haematological disorders even without the presence of clinical signs.

Based on the findings of this study, it can be concluded that *Hepatozoon* spp. was found infecting dogs in the Sertão paraibano mesoregion, affecting all age groups, especially puppies up to 6-months-old, mixed breed animals and those infested with ticks. In most of cases, *Hepatozoon* spp. was not identified as the main cause, but as a secondary laboratory finding, as severe or debilitating clinical conditions were observed in most of the animals studied. It is also suggested that anaemia and thrombocytopenia may be indicative of *Hepatozoon* spp. infection, even in subclinical cases.

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Declaration of interest. The authors inform that there are no conflicts of interest. Authors are solely responsible for the content of the article.

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