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RESEARCH ARTICLE

Evaluation of Hematological, Biochemical Parameters and CRP and PCT Levels in Dogs with *Leishmania Infantum* Detected by ELISA

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ELISA ile Tespit Edilen *Leishmania Infantum*'lu Köpeklerde Hematolojik, Biyokimyasal Parametreler ile CRP ve PCT Düzeylerinin Değerlendirilmesi

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Öz

Amaç: *Leishmania spp.*'nin neden olduğu zoonotik bir hastalık olan Leishmaniasis, köpeklerde çeşitli faktörlerin etkisiyle semptomatik veya asemptomatik bir seyir izlemektedir. Hematolojik ve serum biyokimyasal parametrelerinin leishmaniasis tanısında sınırlı bir rolü olmasına rağmen, hayvanın klinik durumunu, lezyonların şiddetini ve hastalığın prognozunu değerlendirmek için kullanılabilirler. Prokalsitonin (PCT), bir hastalık biyobelirteci olarak sepsis sırasında monositler, nötrofiller, karaciğer, dalak, böbrekler ve akciğerler tarafından salınır. Serum C-reaktif protein (CRP), patolojik durumlarda önemli ölçüde ve hızlı bir şekilde yükselir. Bu çalışmada Leishmaniasisli köpeklerde PCT ve CRP düzeylerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Araştırmanın leishmaniasis grubunu, hastalığın klinik belirtilerini gösteren 157 köpekten ELISA testi pozitif çıkan 9 köpek oluşturdu. Sağlıklı kontrol grubunu oluşturmak için aynı bölgede yaşayan, klinik muayenede sağlıklı olduğu belirlenen, hemogram ve rutin biyokimyasal parametreleri normal sınırlar içinde olan ve ELISA testi negatif sonuç veren 7 köpek seçildi.

Bulgular: Alınan sonuçlarda RBC, Hgb, HCT ve MCHC değerlerinin gruplar arasında anlamlı derecede farklılık gösterdiği tespit edildi. Biyokimyasal ölçümlerin sonuçlarına göre pozitif grupta total protein ve globülin seviyelerinin arttığı, albümin, A/G oranı, sodyum ve klor değerlerinin azaldığı, bu farklılıkların istatistiki yönden gruplar arasında anlamlı olduğu ancak serum PCT ve serum CRP sonuçlarının gruplara göre farklılık göstermediği belirlendi.

Öneri: PCT ve CRP'nin leishmaniasisli köpeklerde klinik biyobelirteç olarak değerlendirilebilmesi için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: CRP, Köpek, Leishmania, Prokalsitonin

Abstract

Aim: Leishmaniasis, a zoonotic disease caused by *Leishmania spp.*, follows a symptomatic or asymptomatic course in dogs due to the influence of various factors. Although hematological and serum biochemical parameters have a limited role in the diagnosis of leishmaniasis, they can be used to evaluate the clinical condition of the animal, the severity of the lesions and the prognosis of the disease. Procalcitonin (PCT), as a disease biomarker, is released by monocytes, neutrophils, liver, spleen, kidneys and lungs during sepsis. Serum C-reactive protein (CRP) increases significantly and rapidly in pathological conditions. This study aimed to examine PCT and CRP levels in dogs with Leishmaniasis.

Materials and Methods: The leishmaniasis group of the study consisted of 9 dogs that tested positive for the disease using the ELISA method, among 157 dogs showing leishmaniasis symptoms. The healthy group consisted of seven dogs living in the same area, which were determined to be healthy through clinical examination, had normal hemogram and routine biochemical parameters, and tested negative in the ELISA test.

Results: : The results showed that RBC, Hgb, HCT, MCV and MCHC values differed significantly between groups. The positive group had higher total protein and globulin levels, while the negative group had lower albumin, A/G ratio, sodium, and chloride values, biochemical measurements revealed. These differences between the groups were statistically significant, however serum PCT and CRP results were not different between the groups.

Conclusion: Further research is required before PCT and CRP can be used as a clinical biomarker in dogs with leishmaniasis.

Keywords: CRP, Dog, Leishmania, Procalcitonin

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Introduction

Leishmaniasis is a zoonotic disease caused by *Leishmania spp.* Dogs are the primary reservoir of the disease for humans. The transmission is mediated by a type of fly called a sandfly (Phlebotominae) (Bates 2007, Morales-Yuste 2022). It can be asymptomatic as well as fatal to dogs. Dogs that continue to be asymptomatic play a crucial role in the transmission of the parasite in the case of leishmaniosis (Molina et al 1994). The symptomatic or asymptomatic course of the disease in dogs can be impacted by factors like age, sex, nutrition, immune system-affecting factors, and other conditions. Susceptibility or resistance of dogs to disease depends on a variety of factors, which have not yet been fully identified (Gomes et al 2008).

Leishmania is diagnosed using molecular methods, serological techniques, delayed hypersensitivity tests, microscopic examination and culture, and serological methods. Despite their limitations in the diagnosis of leishmaniasis, hematological and serum biochemical parameters can be used to assess an animal's clinical condition, the severity of the lesions, and prognosis of disease (Maurelli et al 2020, Freitas et al 2012).

Procalcitonin (PCT) is a small circulating peptide that is synthesized by parafollicular cells in the thyroid gland as a precursor to the hormone calcitonin. During infections or certain pathological conditions, parenchymal cells begin to produce it (Horns et al 2021). In this regard, its application as a biomarker in diseases has recently received a lot of attention. It is secreted by monocytes, neutrophils, the liver, spleen, kidneys and lungs in sepsis (Christ-Crain and Müller 2007). Because the endopeptidases that cause PCT reduction are not found in parenchymal tissues, it circulates as a prohormone. As a result, during infections, serum procalcitonin levels increase significantly in a short period of time (Reinhart and Meisner 2011).

Compared to human studies, PCT research in the veterinary field is still in its infancy. However, recently developed tests in dogs are helpful in determining PCT in sepsis. Serum PCT concentrations in dogs with clinically suspected sepsis are substantially higher than those in healthy dogs (Goggs et al 2018). In addition, higher PCT concentrations have been linked to sepsis, multi-organ failure syndrome, and septic shock (Troia et al 2018), while lower PCT concentrations have been linked to survival in the first 24 hours and recovery from sepsis (Easley et al 2020).

Serum C-reactive protein (CRP) rises significantly and rapidly in pathological conditions. Surgical procedures, traumas, viral illnesses, and systemic inflammation all cause an increase in it (Griebsch et al 2009, Pathak and Agrawal 2019). Despite the fact that there is widespread knowledge in the literature (Daza González et al 2019, Pardo-Marin et al 2020) that it is increased in dogs with leishmaniasis, it has been reported that there is an increase due to organ damage, particularly kidney (Martínez-Subiela et al 2013).

The aim of this study was to investigate the significance of serum CRP and PCT levels in dogs with leishmaniasis in terms of diagnosis and prognosis. There is no research found regarding the PCT level in Leishmania-infected dogs. For this purpose, hematological and biochemical variables, as well as serum CRP and PCT levels, were evaluated. This study serves as a preliminary investigation on the subject.

Material and Methods

Ethical Statement

Tekirdağ Namık Kemal University, Animal Experiments Local Ethics Committee granted permission with decision number 480-T2020.

Selection of Animals

A total of 157 dogs showing more than one clinical symptom compatible with Leishmania, such as anemia, lymphadenopathy, weight loss, emaciation, conjunctivitis, keratitis, onychogryphosis, and skin lesions, were screened. Nine dogs were tested positive in the ELISA test. The dogs that tested positive were selected as the infected group. The healthy group consisted of seven dogs living in the same area, which were determined to be healthy through clinical examination, had normal hemogram and routine biochemical parameters, and tested negative in the ELISA test. In the Leishmania positive group, 4 dogs were male and 5 were female, all of mixed breeds. Their ages were as follows: four were two years old, three were three years old, one was four years old, and one was seven years old. In the healthy group, two dogs were male and the other five were female, all of mixed breeds. Their ages were as follows: two were two years old, one was one years old, two were four years old, and two were five years old.

Sample Collection and Preparation

The blood samples were taken from the vena cephalica antebrachii of the animals, both with and without anticoagulants. The blood smears of Leishmania-positive and healthy dogs were checked for *Ehrlichia spp.*, *Anaplasma spp.*, and *Babesia spp.* using Giemsa staining. The serum and plasma from the blood samples were separated through 15 minutes of centrifugation at 3000 rpm. Before testing, the samples collected were kept at -80°C. Following the manufacturer's recommendations, anti-*L.infantum* antibodies were identified using a commercial ELISA test kit (ID Screen® Leishmaniasis Indirect Test, France). A study determined that the sensitivity rate of the ID Screen® test is 0.953 (Solano-Gallego et al 2014).

Table 1. Hematological findings in healthy and *Leishmania infantum*-infected dogs

		Healthy dogs (n=7)		*L. infantum*-infected dogs (n=9)		
Parameter	Unit	Mean+SEM	Median	Mean+SEM	Median	p Value
RBC	× 10^6/µL	6.541±0.1578	6.54	4.234±0.61	4.6	0.003
Hgb	×10g/L	16.4±0.35	16.4	11.74±1.38	11.9	0.009
HCT	%	40.95±0.97	41.2	25.01±3.81	27.2	0.002
MCV	fL	62.62±0.88	62.62	58.16±1.24	58.3	0.005
MCH	pg	25.10±0.40	25.1	24.19±0.34	24.2	0.133
MCHC	g/dL	34.07±0.19	34.1	34.90±0.39	34.9	0.040
PLT	×10^9/L	336.2±31.62	330	294±128.7	94	0.071
MPV	fL	6.67±0.11	6.7	6.52±0.29	6.5	0.900
WBC	×10^9/L	9.80±0.38	9.5	14.74±3.15	18.2	0.286
Neutrophils	×10^9/L	5.53±0.47	5.5	7.45±1.73	5.2	0.858
Lymphocytes	×10^9/L	2.25±0.27	2.25	4.52±1.34	3.6	0.392
Monocytes	×10^9/L	1.15±0.04	1.15	1.46±0.32	1.1	0.932
Eosinophils	×10^9/L	0.9±0.08	0.8	1.10±0.31	0.9	0.777

RBC: red blood cell, Hgb: hemoglobin, HCT: hematocrit, RDW: red blood cell distribution width, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, PLT: platelet, MPV: mean platelet volume, WBC: white blood cell.

Hematological and Biochemical Parameters

Hematological findings red blood cell (RBC), hemoglobin (Hgb), hematocrit (HCT), red blood cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), mean platelet volume (MPV), white blood cell (WBC), neutrophils, lymphocytes, monocytes, eosinophils were measured using Exigo Eos veterinary hematology analyzer (Exigo-Sweden). Biochemical analysis albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, C-Reactive Protein (CRP), bilirubin, blood urea nitrogen (BUN), phosphorus, potassium, sodium, chloride were measured by Cobas® 6000 (Roche Diagnostik-Swiss) and PCT values were measured by Cobas® e411 analyzer (Elecsys BRAHMS PCT-Roche Diagnostics-Swiss).The manufacturer specifies the sensitivity as 96%, specificity 66%, positive predictive value 78% and negative predictive value 93%, and lower limit of detection 0.02 ng/ml at 0.5 ng/mL cut off value for PCT test.

Statistical Analysis

The Shapiro-Wilk test was used to examine the acquired data's normality test. The GraphPad Prism 9.4.1 package program was used to compare hematological, biochemical, CRP, and PCT values between the control and leishmaniasis groups using non-parametric Mann-Whitney and parametric t-tests. The statistical value considered as $P<0.05$.

Results

The clinical symptoms in the leishmaniasis group of dogs included skin lesions, conjunctivitis, and anemia in four animals; weight loss and anemia in three animals; and weight loss, conjunctivitis, onychogryphosis, and lymphadenopathy in two animals. RBC, Hgb, HCT, and MCV levels ($P<0.01$) were significantly lower in leishmaniasis-positive dogs than in the negative group, but MCHC values ($P<0.05$) were higher. There was no significant difference between the groups in terms of WBC and lymphocyte values (Table 1). When the comparison results of biochemical measurements were examined, it was seen that there was a decrease in A/G ratio, albumin, creatinine, sodium and chloride values, and an increase in T. protein and globulin values in the positive group, and these differences were statistically significant between the groups. The blood PCT level was found to be

Table 2. Biochemical findings in healthy and *Leishmania infantum*-infected dogs

		Healthy dogs (n=7)		*L. infantum*-infected dogs (n=9)		
Parameter	Unit	Mean+SEM	Median	Mean+SEM	Median	p Value
T. Protein	g/dL	7.17±0.20	7.1	8.77±0.28	8.6	0.001
Albumin	g/dL	3.34±0.10	3.35	2.47±0.18	2.44	0.003
Globulin	g/dL	3.82±0.14	3.88	6.31±0.36	6.37	0.0001
A/G ratio		0.88±0.03	0.86	0.42±0.06	0.34	0.0001
ALT	U/L	26.83±1.33	27	30.89±6.12	29	0.858
AST	U/L	39.67±3.99	40	35.0±3.94	32	0.452
Creatinine	mg/dL	0.87±0.05	0.9	0.61±0.03	0.6	0.001
CRP	mg/L	0.37±0.08	0.4	0.40±0.11	0.45	0.825
T. Bilirubin	mg/dL	0.07±0.005	0	0.019±0.012	0	0.483
BUN	mg/dL	19.49±1.18	19.9	22.72±1.08	23.4	0.165
Phosphorus	mg/dL	5.13±0.40	5.34	4.35±0.16	4.22	0.174
Sodium	mmol/L	148.5±1.26	148	138.7±2.60	139	0.002
Chloride	mmol/L	103.6±0.61	103.9	95.6±1.89	94.7	0.002

A/G: albumin/globulin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-Reactive Protein, BUN: blood urea nitrogen.

below the device's lower detection limit of 0.02 ng/ml in both groups, and the serum CRP results were not different between the groups (Table 2).

Discussion

Leishmaniosis is a zoonotic disease. It is also dangerous for humans that asymptomatic dogs continue to be active in the transmission of the parasite. Fontes et al. (2021) reported that skin rashes, weight loss, onychogryphosis, conjunctivitis, keratitis, lymphadenopathy, and splenomegaly are common clinical symptoms in dogs with leishmaniasis. Similar clinical symptoms were also detected in our study. Therefore, it is important to be able to effectively monitor the course of the disease in dogs. PCT begins to be produced by parenchymal cells during infections or in some pathological conditions. With this aspect, its use as a biomarker in diseases has been intensively researched recently. Studies on PCT in veterinary medicine are relatively new compared to human studies. CRP in serum is one of the positive acute phase proteins that increase significantly and rapidly in pathological conditions. In the present study, hematological and biochemical parameters as well as serum CRP and PCT levels were determined and evaluated in dogs with *Leishmania infantum*. It has been reported that the majority of the typical leishmaniasis findings are associated with hematological system diseases. Anemia is one of the most prevalent symptoms of this system and may be brought on by an imbalance between the production and destruction of erythrocytes, or it may be brought on by inflammation, hemorrhage, hemolysis, renal failure, bone marrow aplasia or hypoplasia (Nicolato et al 2013). In comparison to healthy animals, animals with leishmaniasis had significantly lower RBC, Hgb and HCT values. It was suggested that this might be related to a decline in erythropoiesis or the development of hemolysis. Our findings were consistent with those of Amusategui et al (2003), who noted that one of the findings in symptomatic dogs was decreased hemoglobin, hematocrit, and RBC count. The low MCV value in leishmaniasis-infected animals further suggested that the anemic picture was microcytic. The MCHC values in the leishmaniasis group were higher than those in the control group, and this difference was statistically significant. Hemolytic anemia may be the cause of this. Non-regenerative anemia, thrombocytopenia, and variations in WBC count are the most typical hematological abnormalities in leishmaniasis. Because of the severe bone marrow parasitism caused by severe leishmaniasis, hematological results are linked to a bone marrow malfunction defined by reduced erythropoiesis (Ulchar et al 2015). Neutrophilia

may be present due to a systemic inflammatory response in canine leishmaniasis. When there are ulcerative cutaneous lesions present, exposure to subsequent bacterial infections may make this more apparent. On the other hand, other leukocyte populations can exhibit quantitative or qualitative morphological alterations, lymphopenia, lymphocytosis, and, less frequently, eosinophilia (Paltrinieri et al 2016). Although there was no statistically significant difference between the groups in the current study, dogs with leishmaniasis had significantly higher WBC and lymphocyte values. Neutrophil, monocyte and eosinophil counts were not significantly different between the groups. Studies in literature have reported both an increase in lymphocyte levels (Freitas et al 2012), as well as a decrease. The increase in lymphocytes in our study is consistent with the study of Freitas et al 2012 and differs from the findings of decrease in lymphocyte levels reported by Paludo et al (2007). This increase in lymphocytes is likely related to the immune system's response to the infection.

Leishmaniasis in dogs can manifest differently in each patient depending on their age, sex, diet, host genetics, co-infections and/or concurrent disorders, and immunosuppressive circumstances (Solano-Gallego et al 2009). Dysproteinemia that could be considered typical, predominates in leishmaniosis. Despite the increase in total protein, low albumin levels and a decline in the albumin/globulin ratio are common. The leishmaniasis positive group in our study exhibited a dysproteinemia-like appearance which is consistent with the literature. Despite the fact that the levels of total protein and globulin increased, it was found that the albumin level decreased significantly below those of the healthy group. The large increase in globulin levels in the leishmaniasis group could be attributed to immunoglobulins produced in response to the disease (Troia et al 2018).

It was thought that the significantly lower creatinine level in the leishmaniasis positive group compared to the healthy group was due to the weight loss observed in this group, as described in the literature (Braun et al 2003).

It is thought that hyperproteinemia may be the cause of the mild hyponatremia and hypochloremia in the leishmaniasis positive group's electrolyte levels, which were statistically significant.

The levels of bilirubin, ALT, and AST were not statistically different across the groups in terms of liver function. The ALT and AST enzyme levels we found were similar with those found by Freitas et al (2012).

Bacterial infections in humans are known to significantly increase procalcitonin production. Procalcitonin levels are closely connected to the severity and prevalence of the infection. Although it does not increase significantly in local infections, it has been reported that it increases higher in common infections and sepsis, and that sepsis increases procalcitonin levels in dogs (Goggs et al 2018, Troia et al 2018). In a different study (Matur et al 2021), it was discovered that the serum procalcitonin level in dogs with bacterial infections was higher than that in dogs with viral diseases and healthy dogs, and that it increased numerically but not statistically in dogs with parasitic diseases (Ehrlichiosis, Anaplasmosis). In our study, PCT levels were compared between the healthy and leishmaniasis positive groups, and it was shown that both groups' animals PCT values remained below 0.02 ng/ml, the lower limit of the measurement limits. In a similar study conducted in dogs with systemic inflammatory response syndrome (SIRS), it was found that PCT levels increased up to 2000 pg/ml in animals with SIRS, but there was no increase in the control group (Giunti et al 2006).

Since high PCT concentrations are associated with septic shock and multiple organ failure syndrome (Troia et al 2018), the lack of multiple organ failure and sepsis in the infected dogs in our study may explain why PCT levels did not increase. A comparison could not be made since no research, to our knowledge, has been conducted regarding the levels of procalcitonin in canines with leishmaniasis.

Increased PCT levels, however, have been observed in studies of people with visceral leishmaniasis. Severe organ diseases such as hepatomegaly and splenomegaly, as well as clinical signs like fever, are present in those with visceral leishmaniosis (Pasyar et al 2012).

CRP is a non-specific marker by its nature. In a study on dogs with leishmaniasis, it has been reported that no significant increase was observed in borderline proteinuric and non-azotemic group (Grp 2) patients regarding serum CRP levels, even though they found increased and statistically significant levels in proteinuric and non-azotemic group (Grp 3) and proteinuric and azotemic group (Grp 4) patients compared to non-proteinuric and non-azotemic patients (Grp 1) (Martínez-Subiela et al 2013). Our study's normal BUN and creatinine levels demonstrated that there was no azotemic condition in the animals, and the results of our serum CRP analysis agreed with those of the aforementioned study. Leishmaniasis-positive dogs with no clinical symptoms or abnormal clinicopathological findings on physical examination may have CRP levels that are within the normal range, according to the literature (Ceron et al 2018).

Conclusion

This study revealed that anemia developed in dogs with *Leishmania infantum*, along with an increase in total protein and globulin levels and a decrease in Na, Cl, and albumin levels. Measurements of blood PCT and CRP, as well as

liver and kidney function tests, did not significantly change. Further research is required before PCT and CRP can be used as a clinical biomarker in dogs with leishmaniasis.

Conflict of Interest

Authors declares that there are no conflicts of interest related to the publication of this article.

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Ethical Approval

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