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RESEARCH ARTICLE

Evaluation of acute phase proteins and cytokines in dogs with parvoviral enteritis

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Öz

Ok M, Er C, Yıldız R. Parvoviral enteritli köpeklerde akut faz proteinler ve sitokinlerin değerlendirilmesi.

Amaç: Bu çalışmanın amacı parvoviral enteritli köpeklerde akut faz proteinler ve sitokinlerdeki değişimleri değerlendirmektir.

Gereç ve Yöntem: Çalışmanın materyalini 2 - 8 aylık 46 parvoviral enteritli (PVE grubu) ve 8 sağlıklı (Kontrol grup) köpek oluşturdu. Pravoviral enteritli köpeklerde anoreksi, ateş, depresyon, uyuşukluk, kusma ve kanlı ishal belirlendi. Köpeklerde parvoviral enteritis teşhisi dışkı parvovirüs antijen testi ile doğrulandı. Parvoviral enteritis teşhisi konulan köpeklerden kan örnekleri alınarak serum interlökin 1ß (IL-1ß), tümör nekrozis faktör alfa (TNF-α), gama interferon (INF-γ), C-reaktif protein (CRP), serum amiloid A (SAA), fibrinojen ve protein C (PC) düzeyleri ELISA metoduyla ölçüldü.

Bulgular: Sağlıklı grupla karşılaştırıldığında, parvoviral enteritli köpeklerin serum IL-1ß, TNF-α, INF-γ, CRP, SAA, fibrinojen ve PC seviyelerinde istatistiksel olarak önemli artışlar belirlendi.

Öneri: Parvoviral enteritisli köpeklerde serum IL-1ß, TNF-α, INF-γ, CRP, SAA, fibrinojen ve PC seviyelerinde artışların belirlenmesi yangının değerlendirmesinde faydalı olacağı ifade edilebilir.

Anahtar kelimeler: Köpek, parvoviral enteritis, akut faz proteinler, sitokinler

Abstract

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Aim: The aim of the present study was to evaluate the alterations in acute phase proteins and cytokines in dogs with parvoviral enteritis.

Materials and Methods: Aged between 2 - 8 moths, forty-six dogs with parvoviral enteritis (PVE group) and 8 healthy dogs (Control group) were as material in this study. Anorexia, fever, depression, lethargy, vomiting and hemorrhagic diarrhea were determined in the dogs with parvoviral enteritis. Parvovirus infection in dogs was confirmed by examining faeces via parvovirus antigen test. Blood samples were collected from all dogs. Serum interleukin-1ß (IL-1ß), tumor necrosis factor alpha (TNF-α), interferon-γ (INF-γ), C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen and protein C (PC) concentrations were measured by ELISA.

Results: Serum IL-1ß, TNF-α, INF-γ, CRP, SAA, fibrinogen and PC concentrations were statistically significantly increased in the dogs with parvoviral enteritis compared to control group.

Conclusions: It may be stated that increased serum IL-1ß, TNF-α, INF-γ, CRP, SAA, fibrinogen and PC concentrations may be useful in assessing the inflammation in canine parvovirus infection.

Keywords: Dog, parvoviral enteritis, acute phase protein, cytokines

Introduction

Canine parvovirus (CVP) infection is considerable cause of high morbidity and mortality in dogs whelps younger than 6 months (Otto et al 1997, McCaw and Hoskins 2006, Er ve Ok 2015). Canine parvovirus infection has two clinical forms as acute hemorrhagic enteritis and myocarditis. Myocarditis form can develop from infection in utero or in puppies less than 8 weeks old. However acute enteritis form is mostly seen in puppies up to 6 months of age. In myocarditis form, the infected puppies may be found as dead without any symptoms within 24 hours (Prittie 2004, Goddard and Leisewitz 2010). In canine parvoviral enteritis, mortality without treatment has been reported as 91%, however, it is associated with a survival rate as low as 64% with treatment (Kariuki et al 1990).

Serum concentrations of acute phase proteins (APPs) such as C-reactive protein (CRP), serum amyloid A (SAA) and haptoglobulin increase in within a few hours following infection (Eckersallet al 2010). The acute phase response assures reliable markers for diagnosing and prognosticating diseases in both people and animals (Kjelgaard-Hansen and Jacobsen 2011). APPs are synthesized in the liver in response to release of proinflammatory cytokines in diseases such as bacterial and viral infections, immuno-mediated disease, neoplasia, tissue injury (trauma), necrosis and burns (Turgut 2000, Murata et al 2004, Eckersallet al 2010, Kocaturket al 2010). Serum APPs levels have been detected to be eight times more sensitive to inflammatory diseases than white blood cells (Ceronet al 2005).

Clinical applications for APPs have been widely demonstrated prognostication as well as for detection of clinical disease and chronic inflammation (Cary 2011). CRP and SAA have been used in the diagnoses of infection in dogs. Furthermore, increased CRP and SAA concentrations have been detected in dogs with systemic inflammation (Gebhardtet al 2009, Jain et al 2011, Langhorn et al 2014). Serum APPs concentrations have significantly increased in dogs with parvoviral enteritis, especially, CRP seems to be a potent predictor of mortality of diseases (Kocaturk et al 2010).

Endotoxemia have been reported in dogs with parvoviral enteritis (PVE). Bloody diarrhea in parvoviral enteritis results from endotoxemia and cytokine production (Otto et al 1997). Bacterial translocation and coliform septicemia are major factors in the mortality associated with PVE (Isogai et al 1989). Acute phase reaction is alerted by the release of cytokines such as IL-1ß, IL-6 and TNF-α at the site of inflammatory lesions or infections (Bochsler and Slausan 2002, Carry 2013). IL-1ß, IL-6, TNF-α and IFN-γ are produced by inflammatory cells. These proinflammatory cytokines induce local and systemic reactions (Jain et al 2011). It is known that sepsis occurs in dogs with PVE. Serum IL-1ß, IL-6 and TNF-α levels are found to be increased in sepsis. IL-6 may be a reliable indicator of the severity of a systemic bacterial infection (Rau et al 2007). It has been noted that serum IL-6 and TNF-α levels might be valuable for evaluating septic patients (Song et al 2012).

The aim of this study was to evaluate the alteration of acute phase proteins and cytokines in dogs with PVE.

Materials and Methods

The institutional ethical committee approved this prospective study. In this study, 46 dogs with PVE (PVE group) and 8 healthy dogs (Control group) were used. Dogs, aged between 2 and 8 months, were brought into the Faculty of Veterinary Medicine, Internal Medicine Department. Clinical examinations were performed for all dogs. Faeces samples were collected from clinically PVE suspected dogs (anorexia, depression, lethargy, vomiting and hemorrhagic diarrhea) by using rectal swab. Faeces samples were evaluated by the quick parvovirus antigen detection test (CPV Ag test, rapidly test kits, Vettek Medical Istanbul, Turkey).

After the diagnosis of PVE, blood samples were collected from dogs. Blood samples were obtained after centrifugation and stored at -80°C deep freeze until analysis. Canine CRP (Eastbiopharm, China), canine SAA (Eastbiopharm, China), canine protein C (TSZ ELISA, USA) and canine fibrinogen (Eastbiopharm, China) concentrations were measured by ELISA method in Synergy HT multi-mode microplate reader (BioTek Inc, USA) device described by the manufacturer. Measurable sensitivity of CRP is 0.051 mg/L, and test interval of CRP level is 0.1 mg/L and 30 mg/L, measurable sensitivity of SAA is 0.047 µg/mL and test interval of SAA level is 0.1 µg/mL and 40 µg/mL, measurable sensitivity of protein C (PC) is less than 0.15 ng/mL and test interval of PC level is 0.15 ng/ml and 40 ng/mL, and measurable sensitivity of fibrinogen is 0.023 mg/mL and test interval of fibrinogen level is 0.05 mg/mL and 15 mg/mL. Canine IL-1ß (Eastbiopharm, China), canine TNF-α (Eastbiopharm, China) and canine IFN-γ (Eastbiopharm, China) levels were measured by ELISA method in Synergy HT multi-mode microplate reader (BioTek Inc, USA) device described by the manufacturer.

Measurable sensitivity of IL-1ß is 0.1 pg/mL, and test interval of IL-1ß level is 0.2 pg/mL and 60 pg/mL, measurable sensitivity of TNF-α is 0.01 ng/L and test interval of TNF-α level is 0.03 ng/L and 9 ng/L and measurable sensitivity of INF-γ is 2.35 ng/mL and test interval of INF-γ level is 5 ng/L and 1000 ng/L.

All data were presented as mean±SEM. Two sample T test was used to determine the differences between groups (SPSS 19.0 for Windows). The statistical significance level was considered to be $P<0.05$.

Table 1. Concentrations of acute phase proteins in dogs.

Parameters	Control (n:8)	PVE (n: 46)	P value
CRP (mg/L)	2.27±0.19	3.47±0.58	P<0.05
SAA (µg/mL)	2.30±0.52	3.93±0.87	P<0.05
Fibrinogen (mg/mL)	3.08±0.42	4.68±0.65	P<0.05
Protein C (ng/mL)	0.68±0.10	2.10±0.23	P<0.001
IL-1ß (pg/mL)	9.30±0.53	12.9±1.24	P<0.009
TNF-α (ng/L)	0.24±0.76	1.04±0.27	P<0.007
INF-γ (ng/L)	104±0.86	176±23.2	P<0.003

PVE: Parvoviral group, CRP: C reactive protein, SAA: Serum amyloid A, IL-1β: Interleukin 1β, TNF-α: Tumor necrosis factor alpha, INF-γ: Interferon-γ.

Results

Dogs with PVE had anorexia, lethargy, depression, fever, vomiting and hemorrhagic diarrhea. Serum CRP, SAA, fibrinogen, IL-1ß, TNF-α, INF-γ and PC concentrations in dog with PVE and healthy are summarized in Table 1. Serum CRP (P<0.05), SAA (P<0.05), fibrinogen (P<0.05), PC (P<0.001), IL-1ß (P<0.009), TNF-α (P<0.007) and INF-γ (P<0.003) levels were significantly increased in dogs PVE when compared to healthy dogs.

Discussion

Parvoviral infection, one of the most important (lethal) diseases among infectious diseases of dogs, is very difficult to treat. Anorexia, depression, lethargy, fever, tachycardia and tachypnea, vomiting, diarrhea (that can change to mucoid or hemorrhagic) are the common symptoms among dogs with PVE (Pollock and Coyne 1993, Ok et al 2000, Yesilbag et al 2007, Yılmaz and Senturk 2007, Goddard and Leisewitz 2010, Kocaturk et al 2010, Er ve Ok 2015). These symptoms were also diagnosed in this study. The diagnosis of this disease in this study was confirmed by parvovirus antigen test.

This study showed the changes of APPs and cytokines in dogs with PVE (Table 1). APPs are synthesized in the liver in response to release of proinflammatory cytokines in diseases such as bacterial and viral infections, immuno-mediated disease, neoplasia, tissue injury (trauma), necrosis and burns (Turgut 2000, Murata et al 2004). These APPs might be beneficial in determining the disease severity and possibly the response to treatment or prognosis, on a disease-specific basis (Murata et al 2004, Ceronet al 2005, Kjelgaard-Hansen and Jacobsen 2011). CRP and SAA are useful parameters among APPs to indicate inflammation in human and animals (Eckersell and Bell 2010). Increased CRP and SAA concentrations have been detected in dogs with systemic inflammation (Franssonet al 2007, Gebhardt et al 2009, Jain et al 2011, Langhorn et al 2014). CRP and SAA have also been reported to be significantly increased in dogs with PVE (Yule et al 1997, Kocaturk et al 2010). CRP and SAA concentrations significantly increased in dogs with pyometra (Jitpean et al 2014). In present study, CRP, SAA, and fibrinogen concentrations statistically increased in dogs with PVE compared to healthy dogs (Table 1). The reason for this increase in dogs with PVE could be related to an inflammatory process. So, serum CRP, SAA and fibrinogen levels could be important markers for inflammatory process in dogs with PVE. Similarly, several studies have reported that CRP and SAA can be useful markers for diagnosis and prognosis in various diseases (Mastrorilli et al 2007, Gebhardt et al 2009, Jain et al 2011, Mylonakis et al 2011, Langhorn et al 2014). Investigations in people have shown that CRP might be a reliable marker for confirming the presence of early sepsis (Pancer et al 2011). However, CRP and SAA are not specific for detection of bacterial infection, because it is known to increase a variety of diseases (Mastrorilli et al 2007, Gebhardt et al 2009, Jain et al 2011).

In this study, PC activity significantly increased in dogs with PVE compared to healthy dogs (Table 1). Increased activity of PC could be related to insufficient development of hypercoagulable state that occurring disseminates intravascular coagulation or the disease started before 48 hours. Similarly, de Laforcade et al (2008) detected a significant decrease in PC activity from days 1 to 2, followed by a gradual rising in PC activity over time, and this PC activity may remain a useful marker of disease severity in dogs with sepsis. It was reported that PC activity highly decreased in dogs with sepsis (Yan and Dhainaut 2001, de Laforcade et al 2003) and dogs with systemic inflammatory syndrome (Bauer and Moritz 2013). However, Bauer and Moritz (2013) reported increases in PC activity in few dogs with systemic inflammatory response syndrome be interpreted as counter reaction following the activation of the coagulation system due to the inflammatory process. This result was not coincident the results of previous study (Yan and Dhainaut 2001, de Laforcade et al 2003), but this result coincident the results to reported de Laforcade et al (2008).

Cytokines play considerable role in the development and regulation of immune response, thus cytokine profiles contribute to the effect immunity level in the diseases (Ceremi 1992). IL-1ß, TNF-α and INF-γ are produced by inflammatory cells (Jain et al 2011). The release of proinflammatory cytokines such as IL-1ß, IL-6 and TNF-α by monocytes/macrophase and activated T-lymphocyte is considered to be a key event in the development of sepsis (de Boer et al 1992). Bacterial toxins lead to inflammation mediators release from mononuclear phagocytes in sepsis. IL-1ß and TNF-α are important inflammatory cytokines implicated in a variety of disease in dogs (Nakagawa-Tosa et al 1995, Alsemgeest et al 1996, Ohtsuka et al 1997, Baggio et al 2005). It was reported that IL-6 and TNF-α levels significantly elevated in sepsis, and these parameters might be useful markers for evaluating sepsis (Nemzek et al 2001, Rau et al 2007, Song et al 2012). Serum IL-1ß and TNF-α concentrations usually increase in inflammatory disease of dogs (Miyomato et al 1996, Grone et al 2000). Fransson et al (2007) reported that IL-6, TNFα and CRP levels increased in dogs with pyometra and dogs with systemic inflammatory response syndrome. In this study, serum IL-1ß, TNF-α and INF-γ concentrations remarkably increased in dogs with PVE when compared to healthy dogs (Table 1). The reason of increase in IL-1ß and TNFα levels could be related to release of inflammatory mediators against bacterial toxins which occurs in sepsis. Bacterial translocation and coliform septicemia are known to be common reasons in the mortality of dogs with PVE (Isogai et al 1989). Furthermore, INF-γ is produced against viral infection (Nieweldt al 2003). Therefore, selected cytokines such as IL-1ß, TNF-α and INF-γ might be useful indicators in assessing the clinical severity of sepsis in dogs. These results were coincident the results to reported of Miyomato et al(1996), Grone et al (2000), Nemzek et al (2007) and Rau et al (2007).

Conclusion

Increased CRP, SAA, IL-1ß, TNF-α and INF-γ concentrations in dogs with PVE may be accepted to be significant markers of systemic inflammation in parvoviral infection in dogs.

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