Serum pentraxin 3 levels in cats with feline parvovirus infection

Research Article

ABSTRACT

Feline parvovirus (FPV) infection continues to be a serious problem in cats and therefore studies are ongoing to investigate all aspects of the disease. This study was designed to determine the levels of PTX-3 in cats with feline panleukopenia (FPL). Blood samples were taken from 12 cats of different breeds and gender with complaints of weakness, listlessness, anorexia, diarrhoea, vomiting and FPV positive on examination and from 7 cats found healthy on physical and laboratory examination. Whole blood, biochemical parameters, total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSi), serum amyloid A (SAA), C-reactive protein (CRP) and pentraxin-3 (PTX-3) concentrations were determined in both sick and healthy cats. The results showed that there was marked panleukopenia and serum PTX-3 (58.69 pg/mL), SAA (59.91 µg/mL), TOS (14.35 µmol H_2O_2 Eq/L) and OSi (1.17 arbitrary unit) levels were significantly higher in cats diagnosed with FPL compared to healthy subjects. In conclusion, serum PTX- levels were measured for the first time in cats naturally infected with FPV and found to be elevated. Further clinical studies with large numbers of infected cats are needed to clarify these findings and to use PTX-3 as a reliable biomarker in FPV-infected cats.

Keywords: Acute phase proteins, cat, oxidative stress, panleukopenia, pentraxin-3

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INTRODUCTION

Feline panleukopenia (FPL) is a highly contagious infectious disease of all Felidae caused by feline parvovirus (FPV). The disease is widespread throughout the world and mainly affects unvaccinated or partially vaccinated cats, especially kittens, with a high morbidity and mortality rate (Chowdhury et al., 2021; Dinçer and Timurkan, 2018; Truyen et al., 2009). The virus causes systemic infection after faecal-oral contamination. The initial replication site of infection is the oropharyngeal lymphoid tissue and then spreads to other tissues with high affinity to rapidly dividing cells (Awad, 2018; Greene, 2012). The most common clinical signs associated with FPL are anorexia, fever, depression, vomiting, diarrhoae, dehydration and the important consequence is sepsis-related death (Börkü, 2016; Truyen et al., 2009). The most characteristic laboratory finding is panleukopenia with a marked decrease in neutrophils and lymphocytes (Parrish, 1995).

Parvoviral enteritis and associated parameters have been well studied in details in dogs (Mazzafero, 2020), but there are limited number of studies evaluating parameters for diagnosis, prognosis and disease severity in cats with FPV (Petini et al., 2020).

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The status of some parameters such as C-reactive protein, serum amyloid A (SAA), haptoglobin, cholesterol, total thyroxine (tT4), complete blood count (leukocyte and their fractions, erythrocytes, thrombocytes etc.), blood chemistry (albumin, potassium etc.), redox balance (Vitamins D and E, glutathione peroxidase, superoxide dismutase, total antioxidant capacity, malondialdehyde) were related to progression and severity of the disease (Khoshvaghti and Nojaba, 2022; Kruse et al., 2010; Petini et al., 2020; Proporata et al., 2018). Recent studies revealed that the acute phase response develops after infections as a part of the innate host defense system that precedes the acquired immune response (Ceron et al., 2005; Paltrinieri, 2007; Schmidt and Eckersall, 2015) and has been used to assess FPL cases (Petini et al., 2020). However these studies are very limited both in number and content.

Pentraxin 3 (PTX-3), an acute phase proteins, has recectly gained attraction in human medicine in evaluating diagnosis, prognosis and severity of various diseases (Arslanoğlu, 2012; Bastrup-Birk et al., 2013; Liu et al, 2014). Pentraxin-3 (PTX3) plays a crucial role in innate immunity in inflammatory process (Zlibut et al., 2019), and its production in cells is particularly induced by inflammatory stimuli such as TNF-α and IL-1ß, and is stored in neutrophil granules (Günaştı et al., 2017). The main source of PTX-3 is also myeloid dendritic cells. It is produced by many cells such as fibroblasts, endothelial cells, monocytes, macrophages, smooth muscle cells, renal epithelial cells, synovial cells, chondrocytes, adipocytes and alveolar epithelial cells in response to proinflammatory cytokines (TNF-α, IFN-γ, IL-1ß, IL-8, IL-10), microorganisms and microbial products and has been reported to be associated with disease severity (Öztelcan, 2010). PTX-3 is a multifunctional protein and plays important roles in microbial recognition, immune regulation and tissue repair (Asgari et al., 2021). PTX-3 has been reported to inhibit and eliminate viral pathogens by binding to the sialic acid in the structure of PTX-3 and to haemagglutinin on the viral surface, thereby preventing its entry into the host cell, particularly dendritic cells, and binding to epithelial cells, and inducing antiviral immunity by regulating T-cell functions. It has also been reported that inhibition of the viral neuraminidase glycoprotein by PTX-3 prevents the release of newly formed viral particles from infected host cells. PTX-3 has also been shown to facilitate opsonisation and clearance of infected cells (Balhara et al, 2013; Deban et al, 2010; Perez 2019; Reading et al, 2008).

The fact that serum PTX-3 levels are less influenced by other inflammatory conditions and that plasma levels peak rapidly during infection has made it attractive for diagnostic and prognostic purposes in many pathological conditions. It has been shown that there is a positive correlation between the increase in plasma concentration and the severity of the disease (Inoue et al, 2011; Norata et al, 2010; Ristagno et al, 2019). However, to date there appear to be no studies on the status of PTX-3 in FPV-positive cats. Therefore, this study was designed to evaluate the concentrations of PTX-3 in cats infected with feline parvovirus infections.

MATERIALS AND METHODS

Animals

The animals used in this study were admitted to the Teaching Hospital of Faculty of Veterinary Medicine, Aksaray University and the Aksaray Private Veterinary Clinic for treatment or routine health checks. Written informed consent was obtained from the owners of each animal. The study was approved by the Local Ethical Committee for Animal Experimentation, Aksaray University.

The study involved 12 FPL positive and 7 healthy cats. Cats admitted with complaints of

anorexia, diarrhea, vomiting, fever lethargy and dullness and tested positive for FPV antigen (Vcheck V200, South Korea) were allocated to the FPL group. Those with no abnormal laboratory and clinical signs of any disease and tested negative for FPV antigen were assigned to the healthy control group. All cats in the FPL group received standard treatment for 7 days, including crystalloid fluid (isotonic saline, 44 mL/kg/day intravenously-IV, Polifeks perf., Polifarma, Türkiye), antibiotics (metronidazole, 25 mg/kg/day, IV, Polygyl %0.05 perf., Polifarma, Türkiye and amoxycillin+clavulanic acid, 20 mg/kg/day subcutaneously-SC, Synulox enj., Zoetis, Türkiye), supplemental therapy (inactive parapoxvirus extract, 1mL/cat, SC, Zylexis, Zoetis, Türkiye) (Greene, 2012).

Sampling

Blood samples were taken from all cats on admission, followed by rectal faecal swabs. Blood from each cat was collected from the cephalic vein into plain and EDTA-treated tubes (BD microtainer, Switzerland) for biochemical and haematological analyses. Serum was collected after centrifugation at 5000 rpm for 10 min and stored at -80°C until analysis.

Laboratory analyses

Faecal samples were tested in accordance with the manufacturer's instructions (Vcheck V200, Kore) and results were recorded as positive or negative.

Blood samples were analysed for complete blood count on a cell counter (Mindray BC30, Chine) for total leukocytes (WBC), erythrocytes (RBC), platelets (PLT), haemotocrit (HCT), haemoglobin concentration (HGB), neutrophils (NEU), lymphocytes (LYM), monocytes (MON) and eosinophils (EOS).

Biochemical analyses included alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transrase (GGT), blood urea nitrogen (BUN) and creatine (CRE) were performed on an automated analyser (FUJI DRI-CHEM NX600V IC, Japon). Acute phase proteins; C-reactive protein (CRP) and Serum amyloyid A (SAA) were determined using an automated analyser (Vcheck V200, South Korea).

Serum total oxidant status (TOS) and total antioxidant status (TAS) were measured calorimetrically (PowerWave XS, BioTek, Instruments, USA) using commercially available test kits (Rel Assay Diagnostics, Gaziantep, Türkiye) based on the method developed by Erel (2005). TAS was expressed as mmol Trolox Eq/L and TOS as µmol H_2O_2 Eq/L. Oxidative stress index (OSI) was calculated as OSi (arbitrary unit) = [(TOS, µmol/L)/(TAS, µmol Tro equivalent/L) × 100 (Gökçe et al., 2022).

Serum pentraxin-3 (PTX-3) was measured spectrophotometrically (PowerWave XS, BioTek, Instruments, USA) using a commercially available ELISA kit (Cat Pentraxin-3 ELISA kit, ELK Biotechnology, China) according to the manufacturer's instructions.

Statistical analyses

Statistical analyses were performed using SPSS® (version 26.0, Chicago, IL, USA). Normality of data was tested by Shapiro-Wilk test and visually by histogram and Q-Q graph method. Groups were compared by independent samples t-test when data were normally distributed and by Mann-Whitney U test when data were not normally distributed. The stated sensitivity threshold was 13.5 pg/mL for PTX-3 and 5 µg/mL for SAA. Serum PTX-3 and SAA were tested below the sensitivity stated in the test kits for control cats, therefore these values were not included in the statistical analysis. The level of significance was set at $P<0.05$. Variables are presented as mean ± standard error.

RESULTS

Clinical findings

Of the cats diagnosed with FPL, 8 were female (66.6%) and 4 were male (33.4%). Two of these

cats were vaccinated (16.6%), 1 had unknown vaccination status (8.3%) and 9 were unvaccinated (75%). The mean age of the cats in the FPL group was 7.1 months (range 3-14 months). The mean age of the control group was 7.6 months (range 3-36 months) and all were vaccinated, three were males and four were females.

On clinical examination, common complaints on admission were anorexia (75%, 9/12), latergia (75%, 9/12), vomiting (75%, 9/12), diarrhoea (66.7%, 8/12), purulent nasal discharge (8.3%, 1/12) and no clinical signs (8.3%, 1/12). Of the treated cats, 3 died during the treatment (25%, 3/12).

Laboratory findings

Haematological results showed a significant decrease in leukocytes and their fractions in the FPV group compared to the control group (Table 1). In the FPL group, total leukocytes (1.67±0.44/10^9/L), NEU (0.64±0.24/10^9/L), LYM (1.22±0.23/10^9/L), MON (0.12±0.03/10^9/L) and EOS (0.28±0. 0.06/10^9/L) were significantly lower than those of healthy cats (WBC, 10.96±1.23 10^9/L; NEU, 5.41±0.88/10^9/L, LYM, 3.94±0.52 10^9/L; MON, 0.84±0.12 10^9/L; EOS, 0.76±0.11 10^9/L) (P<0.05).

Table 1. Changes in haemotological parameters in the study groups.

Parameters	Groups	Mean±SE	P value
WBC (10^9/L)	FPL	1.67±0.44	<0.001
	Control	10.96±1.23	
NEU (10^9/L)	FPL	0.64±0.24	<0.001
	Control	5.41±0.88	
LYM (10^9/L)	FPL	1.22±0.23	<0.001
	Control	3.94±0.52	
MON (10^9/L)	FPL	0.12±0.03	<0.001
	Control	0.84±0.12	
EOS (10^9/L)	FPL	0.28±0.06	<0.001
	Control	0.76±0.11	
RBC (10^{12}/L)	FPL	12.02±2.29	0.32
	Control	8.81±0.95	
HCT (%)	FPL	37.64±2.70	0.85
	Control	36.75±3.63	
PLT 10^9/L	FPL	228.27±41.12	0.36
	Control	297.17±64.50	

WBC: Total leukocytes, RBC: Erythrocytes, PLT: Platelets, HCT: Haemotocrit, HGB: Haemoglobin, NEU: Neutrophils, LTM: Lymphocytes, MON: Monocytes, EOS: Eosinophils, SE: Standard error, FPL: Feline panleukopenia

Biochemical anaylses resulted in no significant changes in ALT, AST, BUN and CRE in both groups (Table 2). Only GGT was significantly lower in the FPL group (2.03±0.59 U/L) when compared to the control group (4.37±0.67 U/L) (P=0.02).

Results of acute phase proteins and redox status are given in Table 3. Cats with FPL had serum PTX-3 concentration of 58.69±11.59

pg/mL but the values were not detectable in the control group as the test assay had a sensitivity below 13.5 pg/mL. Smilarly, the serum SAA concentration of FPL was 59.91±10.12 µg/mL and was undetectable in the control cats due to the sensitivity of the assay at 5 µg/mL. Although serum CRP concentrations were higher in cases (5.85±1.27 mg/mL) than in controls (3.46±0.81 mg/mL), this was not significant (P=0.2). Cats with FPL experienced oxidative stress as TOS and OSi values were significantly higher in cases (TOS, 14.35±1.28 µmol H_2O_2 Eq/L; OSi, 1.17±0.15 AU) than in controls (TOS, 9.36±0.22 µmol H_2O_2 Eq/L; OSi, 0.77±0.02 AU) (P<0.05).

Table 2. Changes in biochemical parameters between the groups.

Parameters	Groups	Mean±SE	P value
Alanine aminotransferase (U/L)	FPL	83.08±13.40	0.58
	Control	72.14±10.53	
Aspartate aminotransferase (U/L)	FPL	22.08±1.93	0.49
	Control	24.57±3.19	
Gamma glutamyl transferase (U/L)	FPL	2.03±0.59	0.02
	Control	4.37±0.67	
Blood urea nitrogen (mmol/L)	FPL	4.99±0.39	0.39
	Control	5.94±0.97	
Creatine (µmol/L)	FPL	33.08±7.37	0.81
	Control	30.44±5.14	

SE: Standard error, FPL: Feline panleukopenia

Table 3. Changes in acute phase protein and oxidative parameters measured in groups.

Parameters	Groups	Mean±SE	P value
PTX-3 (pg/mL)	FPL	58.69±11.59	-
	Control	UD	
SAA (µg/mL)	FPL	59.91±10.12	-
	Control	UD	
CRP (mg/mL)	FPL	5.85±1.27	0.20
	Control	3.46±0.81	
TOS (µmol H_2O_2 Eq/L)	FPL	14.35±1.28	0.01
	Control	9.36±0.22	
TAS (mmol Trolox Eq/L)	FPL	1.28±0.04	0.33
	Control	1.22±0.02	
OSI (Arbitary Unit)	FPL	1.17±0.15	0.02
	Control	0.77±0.02	

UD: Undetectable, -: No statistic was applicable, PTX-3: Pentraxin-3, CRP: C-reactive protein, SAA: Serum amyloyid A, TOS: Serum total oxidant status, TAS: Total antioxidant status, OSI: Oxidative stress index, SE: Standard error, FPL: Feline panleukopenia

DISCUSSION

Feline panleukopenia is of great concern to cat owners and shelters because of its high mortality and difficulty of treatment. Studies have been undertaken to elucidate the pathogenesis of the disease and thereby predict its outcome (Börkü,

2016; Chowdhury et al., 2021; Dinçer and Timurkan, 2018; Truyen et al., 1996). In the present study, we aimed to determine serum levels of PTX-3, a novel biomarker for predicting disease severity and prognosis, in cats infected with FPV.

In the present study, the majority of cases (75%) were in unvaccinated cats and also about 1 in 5 cases were vaccinated as reported previously (Porporato et al., 2018), which is an alarming finding in both circumstances, as it not only indicates the importance of vaccination in prevention, but also requires more attention to the vaccine and vaccination process. The clinical signs (anorexia, vomiting, diarrhoea, dehydration etc.) and haematological findings (panleukopenia) observed were consistent with previously reported studies (Greene 2012; Parrish, 1995; Truyen et al., 2009). These findings are known consequences of pathogenesis of FPL (Greene, 2012). Biochemical parameters also did not change significantly as previously reported (Porporato et al., 2018), which is unexpected given the organs affected by FPV. It can be speculated that the stage of the disease when the cases were admitted to hospital which might have allowed earlier intervention and the age of the cases presented (mainly young adults and adults) who might be expected to be more resistant, may have played a role. This speculation may also be supported by the higher survival rate (75%), as it can be assumed that the organ damage might not have been severe enough to cause biochemical changes.

Like many other infectious agents FPV is also known to cause inflammation in various host tissues, where it causes cellular damage followed by organ dysfunction (Aydoğdu et al., 2018; McMichael, 2007). Oxidative stress has been reported to be involved in cellular damage in parvo viral infections in dogs (Aydoğdu et al., 2018). This was also the case in our study, as a reflection of oxidative stress TOS and OSi levels were significantly higher in FPL cats when compared to healthy cats. Similarly Khoshvaghti and Nojaba (2022) reported decreased antioxidants (gluthatione peroxidase, vitamin D) and increased malondialdehyde an indicator of cell wall damage in FPV infected cats. These findings may further support the idea that oxidative stress may play a key role in the pathogenesis of FPL.

Previous studies have shown that infectious agents induce an acute phase response in the host, leading to an increase in serum acute phase proteins such as PTX-3, SAA, CRP and haptoglobulin, in an attempt to limit inflammation and tissue damage and to eleminate infectious agents (Bastrup-Birk at al., 2013; Ceron et al., 2005; Gökçe et al., 2009; Hamed at al., 2017; Liu et al., 2014; Paltrinieri 2007, Reading et al., 2008; Perez, 2019; Petini et al., 2020; Schmidt and Eckersall 2015). Therefore, acute phase proteins are commonly used to determine the diagnosis and prognosis of many infectious diseases (Ceron et al., 2005; Gökçe et al., 2009; Liu et al., 2014; Hamed at al., 2017; Perez, 2019). A previous study by Petini and colleagues (2020) reported higher concentrations of haptoglobulin and SAA in surviving cats with FPL, but CRP was not markedly changed, but a study by Gülersoy and colleagues (2023) reported higher serum CRP levels in FPL cases than control. Similar results were found in our study, where cats diagnosed with FPL had significantly higher levels of SAA, but this increase was not significant for CRP.

In the present study, PTX-3 was measured for the first time in cats with FPL. Serum PTX-3 was higher in the diseased cats than in the control cats in which PTX-3 was undetectable. The increase in serum PTX-3 was consistent with the previous studies conducted in other species (Aygün and Yıldız, 2018; Hamed et al., 2017; Koç, 2021; Ramery et al., 2010; Townsend and Singh, 2021;

Wang et al., 2020). PTX-3, a multifactorial acute phase protein, is synthesised and released during inflammation induced by various factors, including infectious agents. PTX-3 synthesis and release is initiated by proinflammatory cytokines (IL-1β, TNF-α), lipopolysaccharide (LPS), various microbial moites and microorganisms (Kunes et al., 2012). During the inflammatory process PTX-3 activates the classical, alternative and lectin pathway of the complement system (Günaştı et al., 2017). PTX-3 recognises most microorganisms including viruses and activates a number of antimicrobial effector mechanisms. Its interaction with P-selectin in the inflammatory response plays an immunoregulatory role and modulates complement system activation (Foo et al., 2015). In sepsis, a condition that can lead to multiple organ failure, as in FPL, PTX-3 is thought to play a major role in early diagnosis and follow-up of the disease process, as PTX-3 is not affected by IL-6, serum PTX-3 levels reflect the severity of the infection and are less affected by other inflammatory effects that may develop simultaneously (Aygün and Yıldız, 2018; Hamed et al., 2017).

The main limitations of this study were the limited number of sick and healthy cats, the inappropriate sensitivity threshold of the ELISA kit to determine PTX-3 levels in healthy cats, which made it impossible to compare PTX-3 levels between cases and controls, and the undefined PTX-3 levels in cases during and after treatment, which made it impossible to evaluate treatment outcome The lack of comparable data is another drawback as this is the first study in this area.

CONCLUSION

In conclusion, the serum concentrations of PTX-3, an acute phase protein, were increased in cats infected with FPV and that PTX-3 levels may be associated with oxidative damage in these cases. Further clinical studies with large numbers of infected cats are needed to clarify these findings and to use PTX-3 as a reliable biomarker in FPV-infected cats.

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