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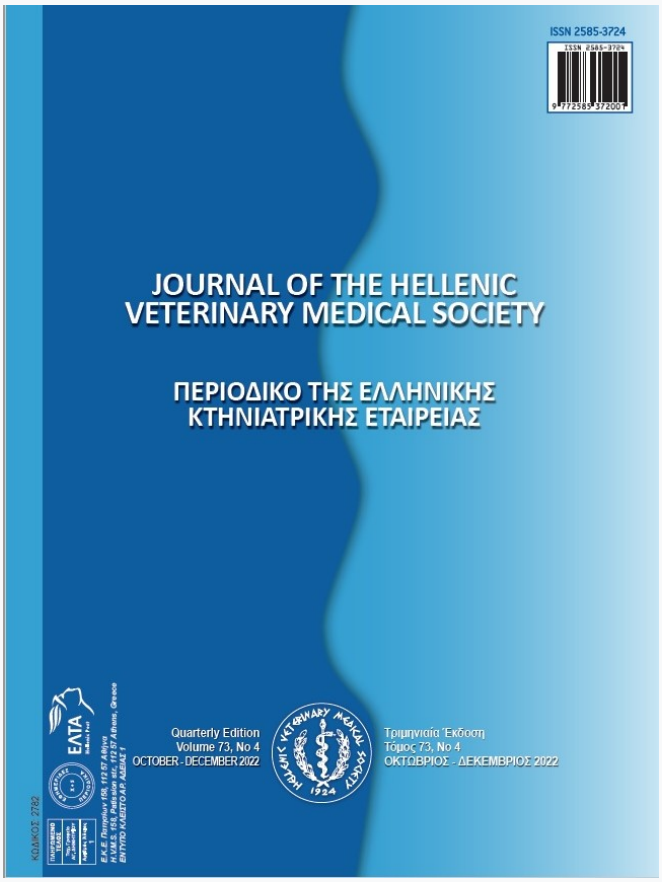

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Investigation of some acute phase proteins, cytokines and hepcidin values in feline enteric corona virus antibodies and feline infectious peritonitis antigen positive cats

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ABSTRACT: Feline Infectious Peritonitis (FIP)is a fatal disease caused by Feline coronaviruses. The causative agent is Feline Infectious Peritonitis Virus, a mutation of Feline Enteric Coronavirus. Feline Corona Virusinfection is very common in the cat population.In Feline Corona Virus infected cats, the development of FIP depends on the cat's immune response. FIP disease is more common in young and old cats because young and old animals have a weaker immune system. The acute phase response is a complex systemic reaction that occurs as a response to acute or chronic inflammatory processes such as infection, neoplasia or immunological disorders, tissue damage, trauma, and surgery. The study material was composed of15 cats with FIP (study group) and 10 healthy cats (control group). Serum amyloid A (SAA), haptoglobin (Hp), α1-acid glycoprotein (AGP), albumin, interleukin-6 (IL-6), hepcidin, alanine-amino transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen(BUN), and creatinine levels were measured in the serum collected from both groups. There was no difference between the wet and dry FIP in albumin values ($p<0.05$).Haptoglobin, α1-acid glycoprotein, SAA, IL-6, and hepcidin values were significantly different between the two groups ($P<0.001$). It was also concluded that hepcidinhas a potential for use as a biomarker in Feline Infectious Peritonitis disease like other acute phase proteins.

Key words: acute phase protein, feline infectious peritonitis, hepcidin

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INTRODUCTION

Feline Infectious Peritonitis is a fatal disease caused by Feline Infectious Peritonitis Virus (FIPV), a mutation of Feline Enteric Coronavirus(FECV / FCoV) (Kim et al., 2016; Riemer et al., 2016). FIP is characterized by two basic forms: granulomatous (dry, parenchymal) or effusive (wet, non-parenchymal). Cats with FIP may have fluid accumulation in abdominal or thoracic cavity or both. Abdominal swelling and fluid accumulation in the abdominal region may manifest with mild fever, weight loss, dyspnea, tachypnea, scrotal enlargement, muffled heart sounds, and mucosal pallor or jaundice (Giori et al., 2011; Riemer et al., 2016). All FECV carriers do not have the potential to develop FIP, only 5% of infections are result in FIP (Foley et al., 1998). Feline Corona Virus (FCoV) is very common in the cat population and usually infects intestines (Kim et al., 2016). All cats carrying FIPV also carry FECV, whereas FIP does not develop in all cats with FECV(Addie, 2000). In Feline Corona Virus infected cats, the development of FIP depends on the cat's immune response. FIP disease occurs mostly in young and old cats because young and older animals have a weaker immune system. This shows the protective effect of the immune system (Pedersen, 2009).

Cats of all ages can be affected.However, approximately half of cats with FIP are less than 2 years of age (Riemer et al., 2016). Antibodies against FECV are found in 80-90% of cats living in crowded conditions and 50% of cats living alone (Foley et al., 1998;Simons et al., 2005). The FIP disease has 2 major forms, one is exudative and the other is a non-exudative form. In some cases, due to the accumulation of body fluids in the terminal stages of the disease in the non-exudative form, mixed form may occur. This final form can only be detected in the necropsy (Hartmann, 2005; Pedersen, 2014).

The diagnosis of FIP is usually performed by symptoms, clinical findings, some abnormalities in diagnostic clinical pathology and most specifically in necropsy and post mortem histopathologic examination. Indirect diagnostic tests for FIP include hemogram, determination of total serum protein, albumin and globulin levels, A:G ratio and some blood chemistries. Common abnormalities seen in hemogram are chronic non-regenerative anemia (anemia of chronic disease) and leukocytosis with an increase in neutrophils and an decrease in lymphocytes.Elevated serum protein associated with high globulins and low albumin, and a low A:G ratio may be seen in blood biochemistry (Pedersen, 2009; Pedersen, 2014).

The A:G ratio has been used as a predictor in the diagnosis of FIP infection. However, the predictive value of the A:G ratio is affected by the presence of another disease and clinical or concomitant biochemical disorders associated with the disease. In a study, it was reported that, if the prevalence of FIP is low, a high A:G ratio is useful to rule out FIP, but a low A:G ratio is not (Jeffery et al., 2012; Pedersen, 2014).

The acute phase response is a complex systemic reaction that occurs as a response to acute or chronic inflammatory processes such as infection, neoplasia or immunological disorders, tissue damage, trauma and surgery(Gruys et al., 2005). The response and production of acute phase proteins varies according to animal species (Petersen et al., 2014). Before the occurrence of specific immunological changes, acute phase response can be used as an early marker of disease (Ceron et. al., 2005; Petersen et al., 2014). Serum amyloid A, α1-acid glycoprotein and haptoglobin are known as acute phase protein reactants in cats (Ceron et. al., 2005; Sasaki et al., 2003). In cats the most commonly used acute phase proteins are C-reactive protein, serum amyloid A, α1-acid glycoprotein, haptoglobin and albumin (Kann et al., 2011).AGP has been used extensively, as an indicator for FIP (Pedersen, 2014).

Hepcidin is a hormone with multiple functions. In the first reported studies, hepcidin was named as an antimicrobial with a peptide structure in human blood and urine (Krause et al., 2000; Park et al., 2001), but in later studies it was reported that it was type II acute phase reactant and had a role as regulator in iron metabolism (Frazer et al., 2002; Laftah et al., 2004; Nicolas et al., 2002). Hepcidin was found to be secreted mostly from the liver and lung and kidney, but not in other tissues (Fry et al., 2004).

Hepatic hepcidin production is under the influence of many stimulants. Low levels of iron and some cytokines, especially with the effect of the IL-6, level of hepcidin increases (Kemna et al., 2005; Lee et al., 2005; Wessling-Resnick, 2010). In one study, applied lipopolysaccharide injection in 10 healthy volunteers and created human endotoxemia, then they found that IL-6 levels were increased in the serum 3 hours after injection, 6 hours later the levels of hepcidin in urine increasedand and followed by a significant decrease in serum iron levels (Kemna et al., 2005).

This study aimed to investigate some cytokine and acute phase proteins (IL-6, SAA, Hp, AGP, albumin) and hepcidin levels in cats with Feline Infectious Peritonitis disease.

MATERIAL AND METHODS

This research was carried out on the basis of the permission of Mehmet Akif Ersoy University Local Animal Ethics Committee dated 09.03.2016 and numbered 176.

Sample Population: The diseased population consisted of 15 cats of different ages and gender with suspicion of FIP infection which were positive for both antibody against FCoV (FcoV Ab Test Kit, BIONOTE, Korea) and antigen against FIPV (FIP Ag Test, Biotech Co., Ltd, Shanghai, China) by rapid test kits using immunochromatography method.The cats used in this study were brought to Veterinary Hospital of our University.

The control group consisted of 10 healthy cats of different ages and gender that were brought to the Veterinary Teaching Hospital for general health check.

All cats were examined with coccidia oocysts and giardia cysts, as well as by rapid test for the presece to Feline Immunodeficiency Virus (Bionote, Antigen FIV Ab), and Feline Leukaemia Virus antigen (Bionote, FeLV Ag) and Panleukopenia Virus (Bionote, Ag) following kits instructions. All analyses were carried out at the veterinary clinic within an hour of taking the blood samples.

Laboratory Methods: Blood samples were drawn from the cats with corona virus antibody and FIP antigen positive and also from the control group. After clotting, samples were centrifuged for 5 min at 4000 xg. Serum samples were removed and stored at -20° C until assayed. The owners of the animals in the study were informed about the applications.

After collecting serum samples from cats in both study and control groups, haptoglobin (Cat Haptoglobin ELISA Kit, Catalog No: MBS 564004), serum amyloid A (Cat SAA ELISA Kit, Catalog No: MBS 007673), α1-acid glycoprotein (Catα1-acid glycoprotein ELISA Kit, Catalog No: MBS 070251), Interleukin-6 (IL-6 ELISA Kit, Catalog No: MBS 085030) and hepcidin (Cat Hepcidin ELISA Kit, Catalog No: MBS 104477) values were measured by ELISA.

ALT, AST, ALP, albumin, BUN and creatinine (Autoanalyzer mod. Gesan chem 200 S / N 1102422 model) values were also determined. Complete blood counts of cats in both groups were performed (Diatron Abacus Junior Vet Hematology Analyzer, S / N 130702 model). At the end of the analysis, both study and control groups were compared statistically.

Statistical Analysis: One-way anova and Duncan tests were used for statistical analysis. Values of $p < 0{,}001$ were considered to be highly significant. SPSS 13.00 package program was used for statistical analysis.

RESULTS

Twenty-five cats initially were included in this study; fifteen in the study group and 10 in the control group. All cats in both groups were panleukopenia, FIV- and FeLV negative, while FcoV (Ab) and FIP (Ag) were positive in cats in diseased group.

The cats included in the diseased group were divided into dry and effusive group according to clinical symptoms and physical examination findings. Of the 15 cats, 9 (60%) showed dry and 6 (40%) effusive form.

Cats with dry form had fever, loss of appetite, weight loss, nystagmus.Ataxia was seen in two cases. In cats showing effusive form had anorexia, depression and fatigue, swelling in the abdomen and ascites. In one case abdominal swelling and edema in the extremities were detected.

Cats in both groups were classified according to age and gender (Table 1). Results of the hematology and biochemistry are shown in table 2 and 3. A significant statistical difference was detected in the investigated biochemical parameters, when compared to the control group in both groups.

Haptoglobin, serum amyloid A, α1-acid glycoprotein, interleukin-6 and hepcidin parameters values were measured by ELISA and the results are shown in table 4.

Table 1. Age and sex distribution of cats in the study and control groups

Age	6 months <	6 months- 2 years	2 years >
Study group	3 (2 female, 1 male)	8 (5 female, 3 male)	4 (2 female, 2 male)
Control group	4 (2 female, 2 male)	3 (2 female, 1 male)	3 (2 female, 1 male)

Table 2. Mean hematological values of cats in study and control groups

	Control Group	Effusive Group	Dry Group	p
WBC (x10³/µL)	8.42±0.31[a]	31.16±3.64[b]	36.36±3.02[b]	<0.001***
RBC (x10⁶)	8.39±0.21[a]	4.99±0.38[b]	3.80±0.42[b]	<0.001***
HGB (g/dL)	11.43±0.37[a]	6.92±0.31[b]	5.89±0.37[b]	<0.001***
HCT (%)	32.17±0.52[a]	21.56±0.50[b]	19.71±0.62[b]	<0.001***
PLT (X10³)	456.90±16.61[a]	284.5±17.13[b]	174.00±30.05[c]	<0.001***

[a,b,c]: There is a statistical difference between the columns containing different letters
[***]: highly significant

Table 3. Mean values of some biochemical parameters of cats in study and control groups

	Control Group	Effusive Group	Dry Group	p
ALT (U/L)	50.70±5.23[a]	125.33±1.78[b]	407.66±6.33[c]	<0.001***
ALP (U/L)	23.90±3.40[a]	91.50±1.23[b]	140.33±3.30[c]	<0.001***
AST (U/L)	21.80±1.69[a]	86.50±2.55[b]	120.66±3.10[c]	<0.001***
BUN (mg/d/L)	22.30±1.06[a]	74.33±1.80[b]	82.55±1.97[c]	<0.001***
Creatinine (mg/d/L)	0.93±0.02[a]	1.56±0.71[b]	2.14±0.12[c]	<0.001***
Albumin (g/dL)	3.4±0.12[a]	1.28±0.21[b]	1.01±0.95[b]	<0.05
Albumin/Globulin	1.00±0.14[a]	0.39±0.07[b]	0.27±0.02[c]	<0.001***

[a,b,c]: There is a statistical difference between the columns containing different letters
[***]: highly significant

Table 4. Mean values of hepcidin with some acute phase proteins in study and control groups

	Control Grup	Effusive Group	Dry Group	p
HP (µg/ml)	455.1± 19.67[a]	4718.6± 530.1[b]	5488.8± 285.26[c]	<0.001***
α1-acid glycoprotein (µg/ml)	200.70± 5.54[a]	2843.10± 87.44[b]	3896.09± 159.39[c]	<0.001***
IL-6 (pg/ml)	30.69± 0.92[a]	60.99± 0.30[b]	70.58± 0.79[c]	<0.001***
SAA (µg/ml)	18.43± 0.18[a]	152.52± 0.31[b]	175.61± 0.70[c]	<0.001***
Hepcidin (ng/ ml)	2.29±0.19[a]	26.54±8.84[b]	16.25±2.19[c]	<0.001***

[a,b,c]: There is a statistical difference between the columns containing different letters
[***]: highly significant

DISCUSSION AND CONCLUSION

Almost half of cats with FIP are under 2 years, although cats of all ages may be affected (Riemer et al., 2016). In our study, 11 of the cats were under 2 years of age (Table 1) which isin agreement with the aforementioned report.

In this study, when the mean hematological values of study and control groups were examined, there was a statistically significant difference in WBC, RBC, HCT and platelet values in cats in two study groups compared to cats in control group. But not significant difference was found between the dry and effusive group for the mentioned parameters.However, significant statistical difference was detected in all three groups in platelet count (Table 2). Cats with FIP are reported to have various haematological abnormalities, with leucocytosis and anaemia being the most common (Hartman, 2005; Riemer et al., 2016). Leukocytosis is characterized by an increase in neutrophils and a decrease in lymphocytes. However, this pattern can be seen in many diseases in cats (Pedersen, 2014). Anemia may occur as a result of secondary autoimmune hemolytic anemia due to autoantibodies against erythrocytes and may also be caused by chronic disease (Hartmann, 2005). In our study leukocytosis in effusive and dry groups were found to be related to infection. Also decrease in parameters such as RBC and HCT related to anemia was consistent with the literature (Riemer et al., 2016). Thrombocytopenia is commonly found in cats with FIP as a result of disseminated intravascular coagulation (DIC) (Hartmann, 2005).In this study according to the hemogram results thrombocytopenia was not seen, but the decrease in platelet count in cats in both wet and effusive groups were statistically significant compared to the control group (Table 2).

In cats with FIP, increase in some parameters (BUN, creatinine, ALT, AST) may vary depending on the degree and location of organ damage (like kidneys and liver), but it has been reported that they will not

help in the etiological diagnosis (Hartmann, 2005). In this study, there were statistically significant differences in ALT, AST, BUN and creatinine values between cats in control group and cats with effusive and dry form in study groups. In cats with FIP, high globulins, hypoalbuminemia, and a low A:G ratio may have been usedin the diagnosis (Pedersen, 2014). In our study there was a statistically significant difference in A:G ratio in cats in control group and cats with effusive and dry form in study groups.

Proteins that show significant changes in blood levels during the acute phase of the inflammation are called acute phase protein (APP). Acute phase proteins are used to assess the response of the body's immune system to inflammation or trauma. They are synthesized from the liver and are mostly glycoprotein(Murata et al., 2004;Petersen et al., 2014). Serum acute phase protein concentrations are increasingly used to monitor inflammatory processes in diagnosis, prognosis and treatment. In cats the most commonly used acute phase proteins are C-reactive protein, serum amyloid A, α 1-acid glycoprotein, haptoglobin and albumin(Kann et al., 2011). In cats, serum amyloid A and α1-acid glycoprotein begin to rise and continue to rise as long as the inflammatory stimulus persists. Haptoglobin is a moderately important APP, and C-reactive protein is not so elevated in inflammatory conditions in cats(Ceron et. al., 2005).

In this study, AGP, SAA, Hp and albumin were measured and C-reactive protein was not used in the study because it was not specific in cats.

AGP measurement may be helpful in the diagnosis of FIP.This acute phase protein is not specific for FIP because it can increase in many infectious diseases in cats (Hartmann, 2005). However, AGP levels in plasma in cats withFIP are generally greater than 1500 µg / mL, which can help to distinguish FIP from other similar conditions (Giordano et al., 2004). It has been reported that AGP plays an important role in the diagnosis of FIP and may also be useful in FIP pathogenesis studies (Paltrinieri, 2008; Pedersen, 2014). In this study, this APP was found to be significantly higher in the wet and dry FIP groupsthan those of in the control group and increase above 1500 µg / mL (Table 4).

It has been reported that the concentration of serum amyloid A may increase 10-fold during inflammatory processes. Therefore, measurement of the concentration of SAA is considered useful for detecting the presence of inflammation (Tamamato et al., 2008). In one study, a 10-fold increase in SAA was observed in cats with FIP, thus confirming the role of serum amyloid A as an APP and suggesting that the high SAA concentration detected in patient cats can be a marker of FIP(Giordano et al., 2004). Similarly, in this study, an increase in the concentration of SAA was found to be approximately 10-fold in FIP cats compared to healthy cats (Table 4).

IL-6 is thought to be one of the main inducers of acute phase reaction and production(Paltrinieri, 2008). In this study, it was found that IL-6 increased significantly in the dry and wet FIP cats compared to the control group, therefore significant increases were observed in all of the APPs compared to the control group.

Hepcidin plays a fundamental role in the regulation of iron metabolism.It has been reported that hepcidin plays an active role in the regulation of iron release from macrophages and control of iron absorption from the duodenum(Murata et al., 2004). Hepcidin plays an important role in the homeostasis of iron in the presence of inflammation in the body, in the storage of iron and in the regulation of erythropoietic activity in the bone marrow. Increased iron levels in tissue and plasma stimulates the expression of hepcidin and reduces iron release from macrophages and hepatocytes. Increased hepcidine concentration in inflammatory or infectious conditions reduces serum iron levels by reducing iron release from macrophages and hepatocytes and limits the release of iron required for microorganisms or tumor cells(Orro et al., 2008). It has been suggested that overproduction of hepcidin during infection and inflammation is the cause of chronic disease anemia(Fleming and Sly, 2001).In our previous study on 56 cattle with single and dual infection (BHV-1, BVDV), hepcidin levels were compared. It was observed that there was a significant difference between the serum hepcidin concentrations of cattle with single and dual infection and the control group of cattle(Şahinduran et al., 2017). In another study, it was reported for the first time that hepcidin value was significantly increased ($p < 0.001$) in dogs with parvoviral infection (52.62 ± 32.09 g/ml) compared to healthy dogs (14.35 ± 16.28 g/ml) (Şahinduran et al., 2016).In a study in calves, we found that hepcidin value increased in calves with viral pneumonia compared to the control group ($P<0.05$) (Dörtkardeş and Şahinduran, 2020).In a study, serum hepcidin concentrations were found to be high in cats with chronic renal failure and this condition was attributed to the inflammatory etiology of chronic renal failure in cats(Javard

et al., 2005). These studies also showed similarity with our study and in our study serum hepcidin concentration was significantly different between healthy animals with cats with dry and wet FIP. In addition, a statistically significant decrease in RBC and HTC values in both wet and dry FIP group compared to healthy cats can be attributed to the role of hepcidin in the regulation of Fe metabolism and to the chronic disease anemia caused by overproduction of hepcidin.

A limitation of our study is that the used FIP Ag Test has not been previously validated independently for use in cats.

As a conclusion, Hepcidin appears to increase in cats with presumptive FIP similarly to other acute phase proteins, and it ha the potential to be used as a biomarker in cats suspected of having FIP.

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CONFLICT OF INTEREST

The authors declare that there have no conflict of interest.

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