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Determination of Haptoglobin, Serum Amyloid A, Some Other Acute Phase Proteins, and Biochemical Parameters in Cattle with Hydatid Cysts

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ABSTRACT The aim of this study is to determine some acute phase proteins and biochemical parameter levels in cattle infected with the hydatid cysts. In the study, a total of 30, Brown Swiss cattle including 15 infected with the hydatid cysts in the study group and 15 in the control group were used. Haptoglobin, serum amyloid A (SAA), ceruloplasmin, interleukin (IL)-6, total protein, albumin, aspartate amino transferase (AST), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) activity, urea, creatinine, iron (Fe) levels were determined colorimetrically. When the animals infected with hydatid cysts and control group were compared, it was determined that haptoglobin, SAA, IL-6, AST, ALP, GGT activity, urea, creatinine levels and acute phase protein index values increased, while albumin levels decreased. In addition, it was determined that the ceruloplasmin and total protein levels increased, globulin, albumin/globulin and Fe levels decreased, but they were statistically insignificant. In conclusion, it was determined that there were significant changes in the biochemical parameters and increased haptoglobin and SAA synthesis in the animals infected with the hydatid cysts, and it is thought that these parameters may contribute to the pathogenesis and diagnosis of the disease.

Keywords: *Haptoglobin, Hydatid cysts, Cattle, Serum amyloid A.*

ÖZ

Hidatik Kistli Sığırlarda Haptoglobin, Serum Amiloid A ve Diğer Bazı Akut Faz Proteinleri ile Biyokimyasal Parametrelerin Belirlenmesi

Çalışmada amaç hidatik kist ile enfekte sığırlarda bazı akut faz proteinleri ve biyokimyasal parametre düzeylerinin belirlenmesidir. Çalışmada çalışma grubunda hidatik kist ile enfekte 15, kontrol grubunda 15 olmak üzere toplam 30 adet Montofon sığır kullanıldı. Haptoglobin, serum amiloid A (SAA), seruloplazmin, interlökin (IL)-6, total protein, albümin, aspartat amino transferaz (AST), gama glutamil transferaz (GGT) ve alkalin fosfataz (ALP) aktivitesi, üre, kreatinin, demir (Fe) düzeyleri kolorimetrik olarak belirlendi. Hidatik kist ile enfekte hayvanlar ile kontrol grubu karşılaştırıldığında, haptoglobin, SAA, IL-6, AST, ALP, GGT aktivitesi, üre, kreatinin düzeyleri ve akut faz protein indeksi değerlerinin arttığı, albümin düzeylerinin ise azaldığı belirlendi. Ayrıca seruloplazmin ve total protein düzeylerinin arttığı, globulin, albümin/globulin ve Fe düzeylerinin ise azaldığı ancak istatistiksel olarak anlamlı olmadığı belirlendi. Sonuç olarak hidatik kist ile enfekte hayvanlarda biyokimyasal parametrelerde önemli değişiklikler, haptoglobin ve SAA sentezinde artış olduğu belirlenmiş olup bu parametrelerin hastalığın patogenezine ve tanısına katkı sağlayabileceği düşünülmektedir.

Anahtar Kelimeler: *Haptoglobin, Hidatik kistler, Sığır, Serum amiloid A.*

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INTRODUCTION

Hydatid cyst is a parasitic zoonotic disease-causing economic loss as a result of expulsion of cystic organs such as liver and lung above all including decrease in meat and milk yield, decrease in wool quality, and increase in infertility rate in farm animals (Balkaya and Şimşek 2010; Acıöz 2018). While the final host of the disease agent Echinococcus granulosus is domestic and wild carnivores such as cats, dogs, foxes and jackals; its intermediate hosts are ruminants, other mammals, and humans (Moro and Schantz 2009; Avcıoğlu 2013). Oncosphere ingested by the host with water and contaminated feed or food forms cysts of various volumes by blood to the liver, lymph lungs, spleen, heart or brain by being released in the intestine (Avcıoğlu 2013; Regassa 2019). The symptoms vary according to the organ where the cysts are located, the number and size of the cysts. The cysts placing in the liver cause jaundice, enlargement of the liver, and ascites and the cysts placing in the respiratory system cause cough, dyspnea, wheezing, and polypnea (Avcıoğlu 2013). Imaging techniques and serological tests are used in order to diagnose the disease in the intermediate host (Gökce et al. 2009; Regassa 2019).

The infectious and non-infectious factors such as inflammation, tissue damage, infection, and toxin cause acute phase response (APR) in the organism. The acute phase proteins (APP), which are nonspecific inflammation markers, are synthesized from the liver as a result of the APR (Abdulkhaleq et al. 2018; Iliev and Geoergiva 2018). Although blood concentration and its importance vary according to the animal species, haptoglobin and serum amyloid A (SAA) are the APPs that have diagnostic importance for cattle. Levels of the APPs are proportional to the extent of the tissue damage and the severity of the disease. In the studies, it revealed that the APPs may be used in differentiation between the bacterial and viral infections, in the differential diagnosis of clinical and subclinical diseases, in parasitic diseases, in the follow-up of treatment efficacy, and in determining the prognosis of sick animals (Tothova et al. 2014). Cytokines are important in the host immunity and their levels may vary depending on the parasite's genus, host type, organ in which it is located and metabolic products (Bayraktar et al. 2005; Abdulkhaleq et al. 2018). While interleukin (IL)-4, IL-6 and IL-10 secreted by T helper (Th)2 lymphocytes are associated with susceptibility to disease in hydatid cysts, IL-2 and interferon gamma secreted by Th1 cells are associated with protective immunity (Rigano et al. 2004). APR occurs depending on the cellular and humoral response in the tissues or organs where the hydatid cyst is located, and ultimately causes changes in APP synthesis in the liver. Therefore, our aim in this study is to determine some APPs (haptoglobin, SAA and ceruloplasmin) and some biochemical parameter levels in cattle infected with the hydatid cysts.

MATERIAL AND METHODS

This study was approved by the Kafkas University Animal Experiments Local Ethics Committee (Approval no: 2021/11).

Animals

In the study, a total of 30, 3-4 years old, Brown Swiss cattle including 15 infected with the hydatid cysts in the study group and 15 in the control group were used. The animals brought to the Department of Internal Medicine, Faculty of Veterinary Medicine, Kafkas University, were clinically examined and diagnosed with hydatid cyst. After slaughter, the diagnosis was confirmed. The control group consisted of clinically healthy animals with the same care and feeding conditions.

Samples

The blood samples from vena jugularis of the animals were taken into tubes without anticoagulant. The samples taken into the tubes without anticoagulant were centrifuged at 3000 rpm for 15 minutes. The serum samples were stored at -20 °C until the analysis would be made.

Determination of Acute Phase Proteins and Biochemical Parameters

Ceruloplasmin levels were determined spectrophotometric method, developed by Colombo and Ricterich (1964), while haptoglobin levels were determined by methods of Skinner et al. (1991). While the SAA and IL-6 level were determined by using the ELISA kit (Tridelta development limited, Ireland; BT Lab, China, respectively), aspartate amino transferase (AST), gamma glutamyl transferase (GGT), and alkaline phosphatase (ALP) activity, urea, creatinine, total protein and albumin levels were found colorimetrically by using the commercial test kit (Biolabo, France). The APP index=[Positive APP (g/dL)/Negative APP (g/dL)]x106 was calculated by using the APP data obtained from the analyzes (Martinez-Subiela and Ceron 2005).

Statistical Analysis

SPSS software program (Version 20, Chicago, Illinois, USA) was used to analyze the data. Since the groups were normally distributed as a result of the Kolmogorov-Smirnov normality test, the student-T test was used to compare the groups. In statistical evaluation, $p<0.05$ value was considered statistically significant.

RESULTS

In the anamnesis, it was learned that various antibiotics were administered to the animals for many times, but no results were obtained from the treatments applied. It was determined that there was atony in the rumen, dyspnea, cough, shallow and rapid respiration (32/min), and tachycardia (92/min) in the heart by the clinical examination. In addition, wheezing of the lung sounds and diffuse dullness in the lung percussion area were detected in the auscultation examination made. Many cysts showing well-circumscribed opacity were detected in the lungs on the radiographic examination made. When the animals infected with hydatid cysts and control group were compared; It was determined that haptoglobin, SAA, IL-6, AST, ALP, GGT activity, urea and creatinine levels ($p=0.001$) increased, while albumin levels ($p=0.021$) decreased. Also, it was determined that ceruloplasmin and total protein levels increased, globulin, albumin/globulin and iron (Fe) levels decreased, but they were statistically insignificant (Table 1). In addition, the haptoglobin/albumin ($p=0.001$) and SAA/albumin ($p=0.010$) index values calculated in the study were found to be higher than the control group (Table 2).

Table 1: Levels of acute phase protein and biochemical parameters in clinically healthy and cattle infected with hydatid cysts.

Parameters	Control ±SEM	Infected with hydatid cysts ±SEM	p
Haptoglobin (g/L)	0.091±0.004	0.155±0.015	0.001
Serum Amyloid A (µg/mL)	16.25±1.23	21.73±1.08	0.002
Ceruloplasmin (mg/dL)	13.56±1.11	17.85±1.82	0.540
Interleukin-6 (pg/mL)	61.94±6.39	165.68±7.08	0.001
Total Protein (mg/dL)	7.02±0.25	6.71±0.16	0.310
Albumin (mg/dL)	3.21±0.13	2.86±0.06	0.021
Globulin (mg/dL)	3.81±0.29	3.85±0.18	0.911
Albumin/Globulin rate	0.99±0.18	0.78±0.05	0.257
AST (U/L)	42.54±2.17	69.49±2.20	0.001
GGT (U/L)	27.41±1.21	49.79±2.84	0.001
ALP (U/L)	28.46±1.16	57.64±3.76	0.001
Urea (mmol/L)	7.24±0.21	9.77±0.54	0.001
Creatinine (µmol/L)	77.03±2.66	134.47±4.24	0.001
Iron (µg/dL)	101.72±3.13	92.66±5.00	0.136

AST: Aspartate Amino Transferase, GGT: Gamma Glutamyl Transferase, ALP: Alkaline Phosphatase

Table 2: Acute phase protein index values of hydatid cysts and healthy cattle.

Parameters	Control ±SEM	Infected with hydatid cysts ±SEM	p
Haptoglobin/ Albumin (g/dL)	2893.54±145.02	5409.61±484.87	0.001
Serum Amyloid A/Albumin (g/dL)	522.38±49.44	765.15±43.05	0.010

DISCUSSION AND CONCLUSION

Symptoms such as cough, dyspnea, wheezing and rapid breathing, tachycardia in cattle infected with hydatid cyst were determined as reported in the studies (Avcıoğlu 2013). The cytokines and other inflammatory mediators are secreted in the hydatid cysts disease depending on the cellular and humoral immune response in the organism because cysts fluid and germinative membrane have antigenic properties in the cysts formed in the intermediate host (Haniloo et al. 2008; Avcıoğlu 2013). It was reported in the studies conducted in the human medicine that the hydatid cysts cause an increase in the cytokine level (Rigano et al. 2004; Bayraktar et al. 2005). In veterinary medicine, a single study was conducted, and it was reported that IL-6 levels increased in cattle infected with hydatid cysts when the infected group was compared with the control group (Sevimli et al. 2015). In the study, it was determined that the IL-6 level increased in the cattle infected with the hydatid cysts. Probably, the reason for the increase may be due to the immunological response against the parasite. The increase in cytokine level depending on the cellular and humoral immune response in the organism causes the APP synthesis in the liver.

Haptoglobin, SAA, and ceruloplasmine are APPs with diagnostic importance for cattle. Haptoglobin, which is very low in the serum of healthy cattle, can increase up to 100 times following inflammation and infection (Pradeep 2014). Studies have shown that in many bacterial (Bozukluhan et al. 2018a; Bozukluhan et al. 2021; Kırbaş et al. 2021), viral (Bozukluhan et al. 2018b; Merhan et al. 2021), parasitic diseases (Bozukluhan et al. 2017; Merhan et al. 2017), and dystocia (Bayyit and Merhan 2020) the level of infection varies according to the type and prevalence. The APPs are nonspecific markers of the tissue damage, and the increase in the haptoglobin level reflects the severity of the infection (Eckersall and Bell 2010). Skinner et al. (1991) defined a serum haptoglobin level in the range of 0.2-0.4 g/L as mild, and between 1-2 g/L as severe infection. In the studies, it was reported that the haptoglobin, SAA and ceruloplasmin levels increased in the mixed-infected goats (Ulutaş et al. 2008), Dictyocaulus viviparus (Ganheim et al. 2004), Cryptosporidium parvum (Enemark et al. 2003), cattle infected with Babesia bigemina (Mohammadi et al. 2021), cattle with hypodermosis (Merhan et al. 2017) and calves infected with Toxocara vitulorum (Bozukluhan et al. 2017). Omidi et al. (2017) reported that there was no significant change in haptoglobin, SAA and albumin levels in a study they conducted in cattle with hydatid cysts. Also, Sevimli et al. (2015) in another study they conducted in cattle with hydatid cysts, they reported that there was an increase in SAA, but the haptoglobin level decreased. In the study, it was determined that haptoglobin and SAA levels increased in cattle infected with hydatid cyst compared to the control group. Skinner et al. (1991) reported that the haptoglobin level was approximately 0.2 g/L, indicating that the severity of the disease is mild. Probably, the reason for this increase may be the tissue destruction in the organs depending on the size of the cysts.

Albumin, which is a negative APP, has functions such as binding and transporting many organic and inorganic molecules (bilirubin, penicillin and calcium, etc.), acting as a source for amino acids, and maintaining the continuity of plasma pressure. It is synthesized by the liver. Its destruction occurs mostly in the kidneys. It was reported that its concentration decreases in liver diseases, anorexia, tissue damage and inflammatory conditions, kidney and intestinal diseases (Tennant and Center 2008). In the study, the albumin level decreased, and it was thought that this may be due to increased albumin catabolism because of inflammation and tissue damage due to infection, or dysfunction due to tissue damage in the liver.

The acute phase protein index is calculated using positive and negative APPs. It has been reported that the calculated index value varies according to the severity and process of the inflammation, and that these changes can be used in the diagnosis of diseases and in the follow-up of healing processes (Martinez-Subiela and Ceron 2005). The index value calculated in the study also increases in relation to the APP concentration, and it is thought that APPs and index values can be used to distinguish between sick and healthy cattle.

Biochemical changes in the blood are used in the diagnosis of many diseases. Studies have reported that parasitic infections cause significant changes in blood parameters and host biochemistry of animals (Ayaz et al. 2006; Irak et al. 2019). Parasitic infections cause damage to the liver tissue and cause changes in the parameters used in the evaluation of hepatic functions such as AST, ALP, GGT and total protein (Sahin and Akgul 2006; Tennant and Center 2008). AST and GGT activity are used to determine liver parenchymal damage, and ALP is used to determine cholestasis (Hoffmann and Solter 2008; Comba et al. 2017). Irak et al. (2019) reported that there was no statistical difference between the groups in terms of GGT, ALT, triglyceride and cholesterol levels in their study in sheep infected with hydatid cyst, but the difference was significant in terms of total protein, globulin and AST activity. In addition, Cinar et al. (2018) reported a significant increase in AST and ALP activity and a decrease in total protein level in another study they conducted in

sheep with hydatid cysts. It is thought that the reason for the increase in AST, ALP and GGT activities in the study may be due to the physiopathological changes in the liver.

Urea and creatinine, which are important parameters in the evaluation of renal functions, are affected by increased protein catabolism in case of infection, as well as the loss of perfusion in the kidneys due to systemic inflammation in infections, resulting in impaired nutrition and functions of the kidneys (Gokce and Woldehiwet 1999; Tennant and Center 2008; Aral 2015). In the study, the reason for the increase in serum urea and creatinine levels may be due to the increase in the rate of protein catabolism or the effect of kidney functions because of systemic inflammation due to the disease.

It was determined that there were significant changes in the biochemical parameters and increased haptoglobin and SAA synthesis in the animals infected with the hydatid cysts, and it is thought that these parameters may contribute to the pathogenesis and diagnosis of the disease.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Idea / Concept: KB, OM
Supervision / Consultancy: GG
Data Collection and / or Processing: ŞK, UA, EA
Analysis and / or Interpretation: TG, DK
Writing the Article: KB, OM
Critical Review: KB, OM, GG

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