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Comparison of some cytokines, acute phase proteins and citrulline levels in healthy and canine distemper infected dogs

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ABSTRACT. Canine distemper virus (CDV) is the etiological agent of severe disease in domestic and wild carnivores. Clinical diagnosis of CDV is challenging because of its similarity to other canine respiratory and intestinal diseases. We aimed to determine certain cytokine (interleukin [IL]-1β, IL-2, IL-4, IL-6, IL-10, and tumor necrosis factor-α [TNF-α]), interferon (IFN)-γ, canine serum amyloid A (SAA), and canine citrulline (CIT) levels for the first time in CDV-positive dogs. For this purpose, 10 CDV-positive dogs with compatible clinical findings (i.e., neurological symptoms such as tremors and myoclonus, ocular and nasal discharge, and wheezing) and 10 healthy dogs based on the clinical examinations and rapid test results were enrolled. It was observed that the CIT, INF-γ, IL-1β, IL-2, IL-6, and TNF-α levels were significantly decreased in the CDV-positive dogs than that of the healthy ones ($P<0.05$). As a result, it was observed that CDV causes immunosuppression and accordingly, the inflammatory response might cause decreased cytokine and acute-phase protein synthesis. Therefore, it was concluded that further investigation of inflammatory pathways and CIT interactions may provide crucial clinical information at different stages of CDV, and aforementioned parameters may serve as important biomarkers for CDV in terms of demonstrating the presence of immunosuppression.

KEYWORDS: canine distemper virus, citrulline, cytokines, dog, serum amyloid A

Canine Distemper virus (CDV), also known as 'Hardpad Disease', is an important viral infection of domestic dogs, wild carnivores such as foxes and ferrets, and sea mammals that affects the digestive, respiratory, and central nervous systems [2]. CDV belongs to the genus *Morbillivirus* in the *Paramyxoviridae* family within the order of *Mononegavirales* [61]. Similar to other morbilliviruses such as *Measles virus* (MeV) and *Rinderpest virus* (RPV), CDV is a lymphotropic and highly immunosuppressive infectious agent. Once the infection occurs, it causes prolonged and severe inhibition and disruption of cellular and humoral immune functions characterised by immunosuppression, lymphocyte loss, and leukopenia, making animals highly susceptible to opportunistic infections [8]. While severe leukopenia during the acute infection phase is typical for many viral infections, morbilliviruses also induce an anergy-like state in immune cells that prevents their *ex vivo* activation by non-specific stimuli leading to loss of delayed-type hypersensitivity responses [40].

Cytokines govern the response of an organism to viral infections. Therefore, the investigation of cytokine expressions and levels is the focus of many studies on viral diseases [4, 56]. Cytokines are small proteins released by various cells in the body, usually in response to an activating stimulus, and respond by binding to specific receptors [15, 60]. One of the earliest responses of the innate immune system to infection and tissue damage is cytokine secretion from tissue cells which is critical for an acute inflammatory response [7]. Viral-induced cytokines, including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, and tumor necrosis factor-α (TNF-α), play a major role in the pathogenesis of emerging diseases and lesions (36).

The antiviral activities of interferons (IFNs) play an important role both in the host's immune response and in the control of viral infections [51]. The IFN system (IFN-α, IFN-β, IFN-γ, and IFN-λ) is present in all vertebrates and is central to antiviral responses [32]. Also, i*n vitro* studies of CDV, MeV, and RPV have demonstrated that P, V, and W proteins can block type I IFN (IFN-α, IFN-β) signalling pathway [5, 47, 53]. Moreover, it was stated that morbillivirus V proteins have the ability to target both type I and type II (IFN-γ) IFN signalling pathways [9]. Although previous studies have demonstrated that morbillivirus blocks the IFN system, the effect of CDV on IFN-γ has not yet been fully elucidated.

The acute-phase response is a highly regulated defence mechanism of vertebrates against infectious agents and attacks. Initiation

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of this response is mediated in macrophages and other leukocytes by endogenous cytokines such as IL-1β, IL-6, and TNF-α induced by exogenous (viral, bacterial) agents that bind to toll-like receptors [14]. Acute-phase proteins are synthesised in the liver in response to proinflammatory cytokine release in conditions such as immune-mediated diseases, tissue damage, bacterial and viral infections, necrosis, and burns [29, 41, 69]. Serum amyloid A (SAA) is one of the acute phase proteins, which are very important for the assessment of prognosis, as well as the detection of the acute or chronic phases of the disease. The detection of these proteins is also useful in terms of their capacity to help increasing the diagnostic sensitivity for inflammatory processes [11, 19, 42].

Canine parvovirus causes severe and widespread damage to enterocytes [38]. It is characterised by an almost complete loss of the intestinal glands and diffuse necrosis of epithelial cells in infected dogs [38]. Citrulline (CIT) is the metabolic product of glutamine and related amino acids, whereas arginine (ARG) [66] is synthesised by enterocytes in the small intestine [68]. The kidneys further recycle CIT to ARG, which is eventually released into the plasma [66]. CIT is the natural precursor of L-ARG, which is the substrate for nitric oxide synthase in nitric oxide (NO) production [52]. Although the liver may contribute to plasma CIT concentration, the intestines remain an important source of CIT in dogs [12]. Serum CIT levels were reportedly low in dogs with parvoviral enteritis [18]. It has also been reported that serum CIT concentration is decreased in dogs with idiopathic inflammatory bowel disease [23]. The CIT level in dogs with CDV has not been previously studied. Experimentally, CIT supplementation in patients with Alzheimer's disease improves spatial memory and increases the level of ARG in the cerebrospinal fluid [35]. This finding indicates that it is worth investigating CIT levels as it may offer new treatment options against CDV as it shows neurovirulence to the central nervous system resulting in poor prognosis and even euthanasia, especially when neurological symptoms begin.

Canine Distemper virus is a worldwide enzootic disease that is difficult to diagnose early due to the variety of clinical symptoms, with very high morbidity and mortality, especially in unvaccinated animals. It is thought that the determination of cytokine levels in the blood serum of CDV-positive dogs may be very important for early diagnosis and can provide information about the disease prognosis and facilitate the determination of appropriate treatment options. In the present study, it was aimed to evaluate the levels of certain cytokine (IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ), acute phase protein (SAA), and CIT levels in CDV-positive dogs.

MATERIALS AND METHODS

Animals and sampling procedure

The animal material of this study consisted of a total of 20 dogs. Of these, 10 dogs were CDV-positive (Trial group) aged 0–12 months of different breeds and sexes (6 male, 4 female, all were intact), and 10 dogs were healthy (control group) as a result of clinical examinations, aged 0–12 months of different breeds and sexes (5 male, 5 female, all were intact). In the selection of animals planned to be included in the study, mostly mixbreed breeds were preferred instead of brachycephalic breeds such as pug, boxer and bulldog, which are known to be prone to the disease. In addition, in the anamnesis, it was learned that dogs with suspected CDV had nonspecific findings such as anorexia, lethargy, fever, vomiting and diarrhea and more specific findings such as myoclonus and tremor for 3–10 days. Also anamnestic data revealed that all dogs included in the present study were unvaccinated, with limited outdoor access for toilet and walking purposes, and fed on commercial dry food. The study protocol was approved by the Ethics Committee of (Veterinary Faculty, Selcuk University, Konya, Turkey, Decision No: 2020-124).

The diagnosis of CDV was confirmed according to the results of a rapid diagnostic test kit (Asan Easy Test CDV Ag®, ASAN Pharm. Co., Ltd., Gyeonggi-do Korea; relative sensitivity: 97.96%, relative specificity: 97.50%) using nasal and ocular discharge samples from dogs with compatible clinical findings including neurological symptoms such as tremors, myoclonus, and nasal and ocular discharge and wheezing that were included in the Trial group (n=10). The control group (n=10) consisted of dogs that were deemed healthy as a result of clinical examinations and CDV rapid diagnostic test results. All the dogs in the present study were brought to the Animal Hospital either for vaccination/routine check-up and diagnosis/treatment purposes.

Cytokine ELISAs

Canine TNF-α (Cat. no: E0025Ca, BT LAB, Shanghai, China), Canine INF-γ (Cat. no: E0011Ca, BT LAB), Canine IL-1β (Cat. no: E0002Ca, BT LAB), Canine IL-6 (Cat. no: E00041Ca, BT LAB), Canine IL-4 (Cat. no: E0003Ca, BT LAB), Canine IL-2 (Cat. no: E0201Ca, BT LAB), Canine IL-10 (Cat. no: E0006Ca, BT LAB), canine serum amyloid A (Cat. no: E0125Ca, BT LAB) and canine CIT (Cat. no: E0231Ca, BT LAB) were evaluated with commercially available enzyme-linked immunosorbent assay kits using serum samples extracted from blood samples obtained using a jugular venepuncture technique from the CDV-positive and the healthy dogs with minimum patient stress. Measurements were performed on an enzyme-linked immunosorbent assay reader (MWGt Lambda Scan 200, Bio-Tek Instruments, Winooski, VT, USA) according to the manufacturer's instructions.

Statistical analysis

The data obtained in this study were evaluated using analysis of variance and a *t*-test as the post hoc test (SPSS 25.0, IBM, Armonk, NY, USA) after the normality test. A *P*-value of <0.05 was accepted as the limit of statistical significance.

RESULTS

The serum levels of IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, canine SAA, and canine CIT of the CDV-positive and the healthy dogs are shown in Figs. 1 and 2. Although there was a decrease in the levels of all measured parameters in the CDV-positive dogs, statistically significant differences were only found in terms of CIT, INF-γ, IL-1β, IL-2, IL-6, and TNF-α levels ($P<0.05$).

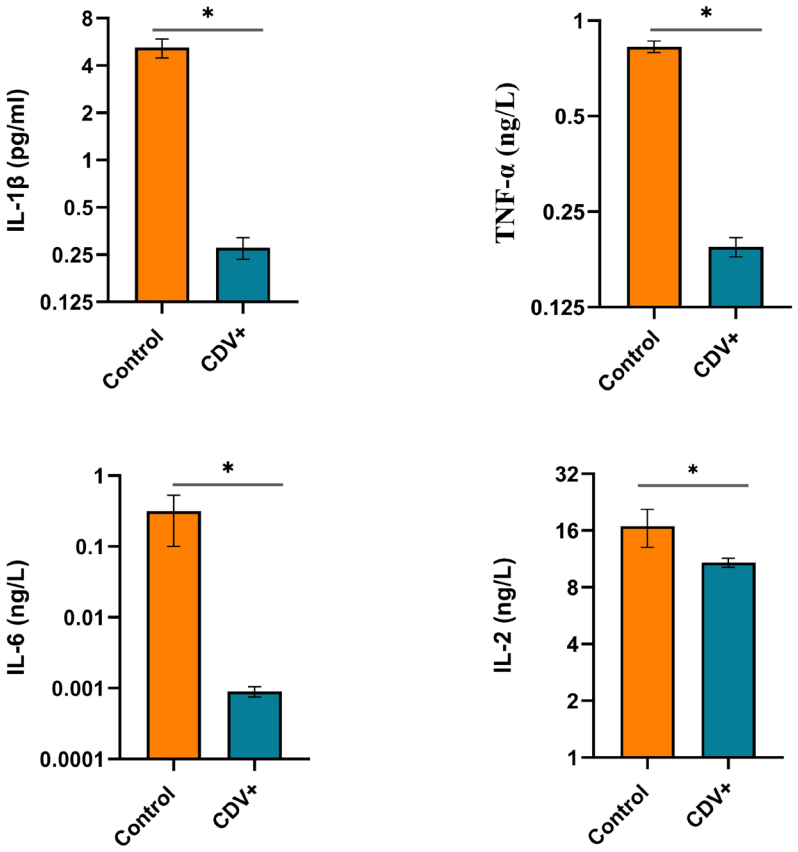

Fig. 1. The changes in interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6) and interleukin (IL-2) levels in canine distemper virus positive (CDV+) and control dogs. Values are expressed as mean ± SEM. The '*' symbol in the columns shows a statistical difference (P<0.05) when compared to the control group.

DISCUSSION

The interaction between cytokines and viruses is complex, as they both suppress the cytokine activity of viruses through various pathways and induce cytokine expression [4, 56]. The role of cytokines in the development and progression of lesions during CDV infection, especially in dogs, is not fully understood. It has been reported that CDV [61], which is from the *Morbillivirus* genus of the *Paramyxoviridae* family, causes an acute immunosuppression, which is a common feature of morbillivirus infections [28]. *In vitro* studies have shown that CDV induces the expression of various cytokines [26]. Analysis of cytokine levels is important for the better understanding of the immune response in CDV-positive dogs. In the present study, the IL-1β, TNF-α, IL-6, IL-2, IL-10, CIT, IFN-γ, and SAA levels in the serum samples of CDV-positive dogs were lower than those of the healthy dogs. Although a decrease was observed in all parameters, a statistically significant difference was determined only in terms of CIT, INF-γ, IL-1β, IL-2, IL-6, and TNF-α levels (P<0.05). It was reported in CDV disease, the virus reaches the central nervous system and gastrointestinal tract by hematogenous route 8–9 days after exposure to the agent [16]. Immunosuppression due to regional lymphocyte apoptosis and both epithelial and enterocyte damage of the gastrointestinal tract may cause low citrulline levels [6]. Therefore, the lower citrulline levels determined in the present study, which differ from previous reports, may be associated with the time to hospital admission (3–10 days after the onset of nonspecific symptoms such as anorexia, lethargy and fever in CDV-positive dogs) and thus the developing enterocyte/epithelial damage in CDV-positive dogs.

In a study by Gröne *et al.* (1998) it was reported that IL-1β levels in seven, IL-6 levels in three, and TNF-α levels in eight out of 14 CDV-positive dogs were high. Moreover, the authors stated that the demyelination seen in the central nervous system of CDV-positive dogs may be caused by the increased expression of IL-1β and TNF-α in the blood [24]. Gröne *et al.* (2004) conducted an *in vitro* study on brain cells, dermal fibroblasts, DH 82 cells (macrophage-like), and epithelial Madin-Darby canine kidney cells, in which IL-1β, IL-6, and TNF-α levels are induced at different levels in a cell-specific manner [26]. In the present study, the finding that IL-1β levels were lower in CDV-positive dogs compared with the healthy dogs (Fig. 1) which overlaps with the finding that MV V proteins inhibit IL-1β secretion in human macrophage-like THP-1 cells by interacting with NLRP3 in the study of Komune *et al.* (2012) on MeV in the Morbillivirus genus. Although IL-1β levels have been reported as an early marker of canine inflammatory processes, low levels may be associated with the extent of the central nervous system injury and the time to hospital admission as the lymph nodes become tissues filled with high viral loads after 2–4 days from contact [45]. In addition, Messling *et al.* (2006) reported that the

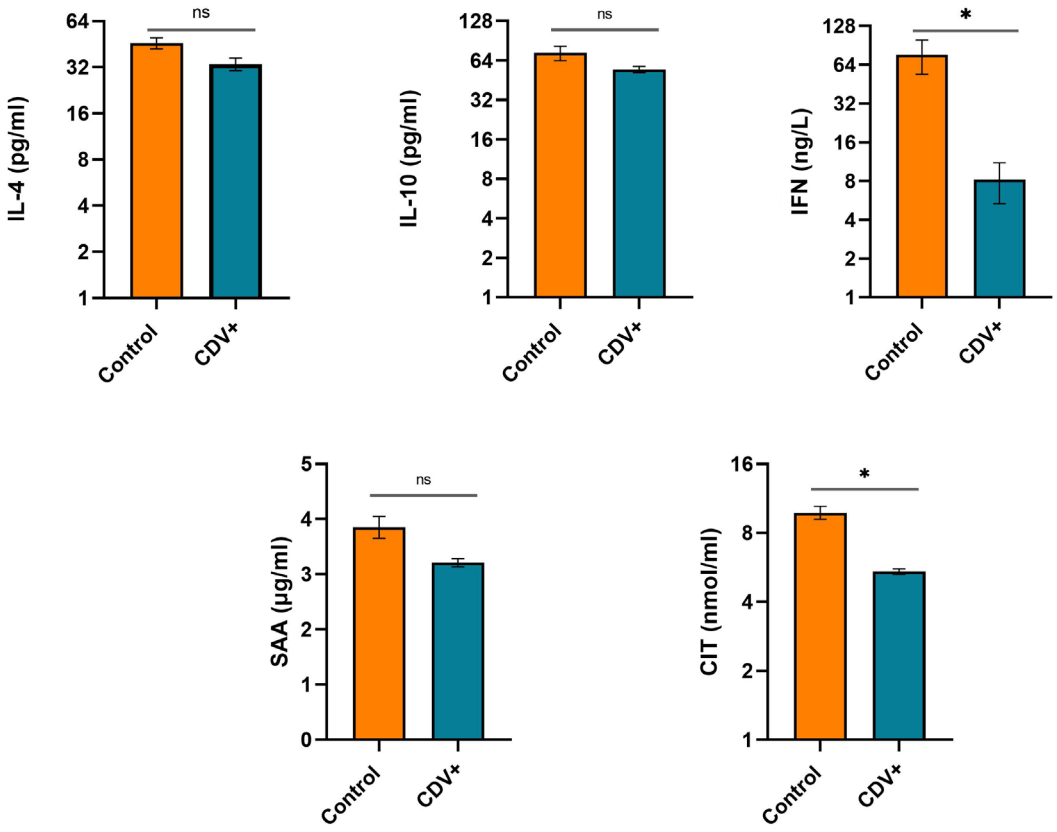

Fig. 2. The Changes in interleukin 10 (IL-10), interleukin 4 (IL-4), interferon (IFN), serum amyloid A (SAA), and citrulline (CIT) levels in CDV+ and control dogs. Values are expressed as mean ± SEM. The '*' symbol in the columns shows a statistical difference (P<0.05) when compared to the control group.

CDV V protein leads to rapid lymphocyte-based invasion of mucosal tissues and lymphatic organs, inhibition of IFN-α/β induction in peripheral blood mononuclear cells, and inhibition of cytokines such as TNF-α, IFN-γ, and IL-6 [37]. In a literature review, it was observed that cytokine expression decreased due to severe immunosuppression in CDV-infected ferrets [25, 57]. CDV, which infects secondary lymphoid organs and prefers lymphoid tissue to reproduce, spreads from tonsil and bronchial lymph nodes to the spleen, lymphoid tissue, and bone marrow by destroying these tissues, leading to a decrease in the number of lymphocytes, suppression of some cytokines, lymphocyte and macrophage dysfunction, and a decreased antibody levels [17]. This immunosuppression contributes to the morbidity and mortality of CDV by causing to emerge opportunistic and secondary infections [50]. In the present study, the statistically significant decrease in terms of TNF-α, IFN-γ, and IL-6 levels in CDV-positive dogs may have developed due to immunosuppression of CDV in lymphoid tissues (Fig. 1).

One of the important components of the cytokine system is IL-10 that regulates and suppresses the expression of proinflammatory cytokines during the healing phase of an infection and consequently reduces the damage caused by inflammatory cytokines [3, 43]. In addition, IL-10 suppresses the ability of dendritic cells and macrophages to stimulate the proliferation of antigen-specific CD4 T cells [39]. Frisk *et al.* (1999) reported that six out of nine CDV-positive dogs had increased IL-10 expression in cerebrospinal fluid cells [22]. Markus *et al.* (2002) reported that the expression levels of proinflammatory cytokines in the central nervous system increased in the brain tissues of CDV-positive dogs showing central nervous system symptoms, and that the increase in IL-10 levels was insignificant [34]. In the current study, the IL-10 levels in CDV+ dogs differed from those reported in previous studies (Fig. 2). The reason the IL-10 level in the current study did not show similarity with previous studies may be due to measurement from different tissues. According to the present results, the IL-10 level in CDV-positive dogs was statistically insignificant but numerically lower than those of the control group. It was interpreted that the MV N protein led to immunosuppression and inhibition of IL-10 by modulating antigen presentation in dendritic cells and interfering with T cell function [33, 55]. In addition, this finding can be explained by the fact that V and C proteins are non-essential for virus replication but critical for counteracting the host innate immune responses [37].

It has been reported that some important morbilliviruses, such as RPV, peste-des-petits-ruminants virus, MeV, and CDV inhibit IFN signalling pathways and block the effect of IFN-α/β and IFN-γ. Morbillivirus proteins V, C, and N can also suppress transcriptional responses induced by IFNs and antiviral responses [9, 59]. In the study by Frisk *et al.* (1999) in which they examined the cerebrospinal fluid of animals with CDV, it was reported that the IFN-γ expression level increased in only one out of 12 dogs. Notably, the IFN-γ levels measured in the serum obtained from CDV-positive dogs in the present study were significantly suppressed compared to those of the control group (Fig. 2). This finding may be related to the fact that the presence of IFN-γ a marker of virus persistence and the

virulence of CDV depends on the suppression of the IFN-γ signaling pathway via interference with MDA5 and STAT2 signaling as the CDV-positive dogs in the present study had both neurological and gastrointestinal clinical findings [58]. Indeed, among the viral proteins in morbilliviruses, it has been reported that the most conserved N protein [44] has nuclear localisation signals in the same location in MV, CDV, and RPV [54]; therefore, their abilities to inhibit IFN-α/β and IFN-γ signals are similar [59]. In addition, morbillivirus V proteins can target IFN signalling pathways to control the effects of both IFN-α/β and IFN-γ [5, 9, 21]. In conclusion, viral proteins are thought to inhibit the antiviral response in cells by blocking (antagonist effect) IFNs, which induce a virus-resistant state in the cells and also play an important role in modulating the adaptive immune system [9].

Acute-phase proteins are synthesised in the liver and are released in addition to proinflammatory cytokines in bacterial and viral diseases [41, 42, 62, 63]. SAA is an acute-phase apolipoprotein of the high-density lipoprotein fraction in plasma. Its physiological role in host defence during inflammation is not fully understood, although it reportedly contributes to functions such as endotoxin detoxification and inhibition of lymphocyte and endothelial cell proliferation, platelet aggregation, and T-lymphocyte adhesion to extracellular matrix proteins [64]. A previous study reported that mean SAA and haptoglobin concentrations were higher in the blood serum of border disease virus-infected goats compared with the uninfected goats [1]. The blood serum SAA level of cows infected with foot-and-mouth disease virus was reported to be increased [36]. In addition, Ok *et al.* (2015) reported that SAA levels increased significantly in dogs with sepsis [42]. Also, in humans, SAA has been shown to be potentially comparable to CRP in terms of diagnostic value, and some studies have demonstrated that human SAA may be an even more sensitive marker of systemic inflammation than CRP [13]. Moreover, in canine patients, it was reported that SAA seems to possess greater diagnostic potential for systemic inflammation compared with serum CRP [10]. SAA, which has a longer half-life than CRP, was preferred for the assessment of acute inflammatory response, since it has not been previously studied in CDV-positive dogs and considering the time to hospital admission [67]. In the present study, the low SAA level in CDV-positive dogs was interpreted as a result of immunosuppression caused by CDV (Fig. 2). However, further detailed studies on this subject are important for understanding the immunopathogenesis of CDV.

NO has strong antimicrobial activity against various DNA and RNA viruses [49]. The level of CIT in CDV-positive dogs has not been investigated *in vivo*. In the present study, the CIT level was lower in CDV-positive dogs than those of the control group (Fig. 2). In murine macrophages activated during mycobacterial infection, ARG synthesis from CIT is required to maintain NO synthesis when extracellular ARG is depleted [46]. A previous study reported that CIT released by the intestines causes intracellular NO production [27, 66]. Therefore, the synthesis of NO from CIT for protection in CDV-positive dogs suggests that it may lead to decreased serum CIT levels. Uzzan *et al.* (2020) reported that plasma CIT concentrations decreased in coronavirus disease 2019 patients and that severe acute respiratory syndrome coronavirus 2 had a direct effect on enterocytes [65]. Lange *et al.* (2017) reported that T cells can regenerate intracellular L-ARG through l-CIT metabolism to mediate inflammatory functions [30]. It has also been suggested that CIT catabolism via the CIT urease enzyme in Francisella tularensis infections plays a role in the production of ammonia, which contributes to the inhibition of phagosomal maturation and the inhibition of NO production through the depletion of CIT [20, 31].

In dogs, among the most common agents to promote viral gastroenteritis are reported to be parvovirus and CDV which causing diarrhea and vomiting. In addition, CDV clinically promotes those affected, multifocal encephalopathies, leukopenia, paralysis, myoclonus, loss of appetite, depression, seizures in severe cases [48]. After compromising the animal's immunity, the presence of the virus causes degradation of the epithelium causing a severe gastroenteritis accompanied by hemorrhagic diarrhea similar to parvoviral enteritis which is characterised by atrophy of the villi with complete collapse of mucosal architecture [18]. Since the primary source of citrulline is enterocytes, the low citrulline levels observed in CDV-positive dogs may be due to enterocyte damage as well as complications such as the development of sepsis and critical illness [16]. However, as a result of the studies carried out to date, the role of CIT in viral infections has not been clearly understood yet. Therefore, further comprehensive studies on CIT in various viral diseases are required.

The present study has some limitations. First, the aforementioned cytokines and acute phase proteins have not been investigated at different stages of the disease. Second, the lack of evidence supporting that CIT levels are specific for CDV can be considered as a limitation, given the fact that CIT is released from enterocytes of the proximal jejunum and duodenum and is uptake by nutritional proteins and additionally metabolized by the kidney. Thus, it is recommended to evaluate CIT levels in naturally developed CDV cases together with nutritional status information, markers indicating kidney and intestinal damage.

In conclusion, we considered that CDV causes decreased inflammatory response due to immunosuppression in the later stages of the disease, and that the cytokines and acute-phase proteins were synthesised accordingly. In addition, serum CIT levels in CDV-positive dogs were determined for the first time in the present study. In future studies, it will be necessary to investigate the inflammatory pathways and interactions of CIT in detail in samples taken at different stages of CDV in terms of demonstrating the presence of immunosuppression.

CONFLICT OF INTEREST. The author(s) declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

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