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Investigation Of Zonulin Levels in Dogs Infected with Canine Distemper Virus

Ethem Mert ÇÖLLÜ[1], Tahip ÖZALP[1] Songül ERDOĞAN[1] Kerem URAL[1] HASAN ERDOĞAN[1]✉
[1] Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Department of Internal Medicine Aydın/Türkiye

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Abstract: This study aims to investigate the impact of Canine Distemper Virus (CDV) infection on plasma zonulin levels, focusing particularly on how this effect varies in patients exhibiting neurological symptoms. The research involved evaluating 20 infected dogs and 10 healthy control dogs, all of which were brought to the Internal Medicine Clinics of Aydın Adnan Menderes University Veterinary Faculty for diagnosis and treatment. In this study, zonulin levels were found to be significantly elevated in patients with gastroenteritis or solely with neurological symptoms compared to the control group. These findings may suggest that the virus affects not only the gastrointestinal barrier but also the blood-brain barrier. This supports the hypothesis that these changes may contribute to the increased permeability of the blood-brain barrier.

Keywords: Distemper, Dog, Gut permeability, Zonulin

Kanin Distemper Virus ile Enfekte Köpeklerde Zonulin Seviyelerinin Araştırılması

Özet: Bu çalışma, Canine Distemper Virüs (CDV) enfeksiyonunun plazma zonulin seviyeleri üzerindeki etkisini, özellikle nörolojik semptomlar gösteren hastalarda nasıl değiştiğini araştırmayı amaçlamaktadır. Araştırmada, Aydın Adnan Menderes Üniversitesi Veteriner Fakültesi İç Hastalıkları Klinikleri' ne tanı ve tedavi için getirilen 20 enfekte köpek ve 10 sağlıklı kontrol köpeği değerlendirilmiştir. Enfekte köpeklerde zonulin seviyeleri, sağlıklı kontrollerden anlamlı derecede yüksek bulunmuştur. Bu bulgular, virüsün sadece gastrointestinal bariyeri değil, aynı zamanda kan-beyin bariyerini de etkilediğini önermektedir. Bu değişikliklerin kan-beyin bariyerinin artan geçirgenliğine katkıda bulunabileceği hipotezini desteklemektedir.

Anahtar Kelimeler: Bağırsak geçirgenliği, Distemper, Köpek, Zonulin.

1. Introduction

Canine distemper virus (CDV) is one of the most common and lethal infectious diseases in dogs. Although it is largely preventable through immunization, it remains a significant cause of mortality and morbidity, particularly in puppies, in shelters and crowded environments. The infection in dogs can range from mild to severe and may result in death in more than 50% of infected dogs (1). As the virus replicates in the lymph nodes, nervous system and epithelial tissue, various systemic symptoms arise. The inflammatory response that occurs plays a role in the development of neurological symptoms (2). Recent research provides strong evidence for the role of the gut-brain axis in the pathophysiology of neurodegenerative diseases (3,4). As a result, the integrity of the intestinal epithelial barrier is considered crucial in the microbiota-gut-brain pathway (5). The junctions between intestinal endothelial cells play a vital role in regulating the mucosal barrier and intercellular permeability. It has been proposed that increased intestinal permeability, along with genetic factors and environmental triggers, is an integral component in the pathogenesis of inflammatory bowel diseases, including allergic, autoimmune and metabolic disorders (6,7). In this context, zonulin is highlighted as regulating the reversible permeability of these junctions, which manage intestinal permeability. Clinical studies have reported that zonulin is effective in identifying intestinal permeability as a biomarker (8,9). Zonulin, a major tight junction regulator in intestinal epithelial cells, also serves as a key protein in maintaining the function of the blood-brain barrier (5). Indeed, during COVID-19 and SARS-CoV-2 infections, zonulin has been reported to increase acute lung injury and the accumulation of neutrophils and cytokines by activating complement C3 and C5 components, which are held responsible for the uncontrolled activation of the complement system during clinical complications (10,11). Zonulin may impair the function of barriers in both brain tissue and the intestine by triggering inflammatory processes, potentially facilitating the spread of viruses (12). The role of zonulin in this process becomes even more critical in the context of neurodegenerative diseases and the neurological complications caused by COVID-19 (13). The potential role of zonulin in SARS-CoV-2 infection is supported by pathophysiological mechanisms linked to the disruption of

✉: hasan.erdogan@adu.edu.tr

the blood-brain barrier and the associated neurological symptomatology (14).

It is hypothesized that CDV infection may contribute to neurological symptoms by affecting intestinal and blood-brain barriers. This study aims to investigate changes in plasma zonulin levels in dogs infected with CDV and to explore the effects of the infection on intestinal permeability.

2. Materials and Methods

This study was conducted with the approval of Aydın Adnan Menderes University Local Ethics Committee for Animal Experiments (HADYEK) under the approval number 64583101/2022/74.

2.1. Animal Material

Twenty dogs with CDV and ten healthy control dogs (aged 1-8 years) examined at Aydın Adnan Menderes University Faculty of Veterinary Medicine were included in the study. The diseased group consisted of dogs diagnosed with CDV using rapid test kits based on immunochromatographic methods, without comorbidities and exhibiting neurological symptoms. The healthy group included dogs that had received at least three doses of multivalent vaccines, underwent regular parasite treatment and were healthy without any specific metabolic diseases. Additionally, pregnant or lactating dogs, as well as those with comorbidities such as chronic liver damage or heart failure, were excluded from the study.

2.2. Methods

Blood samples were collected from the *V. cephalica antebrachii* into vacuum tubes containing lithium heparin using an appropriate technique, following the anamnesis and clinical examinations of the dogs. Upon completion of the hematological and biochemical analyses of the collected blood samples, the remaining samples were centrifuged at 3000 rpm for 15 minutes to isolate the plasma, which was then stored at -80°C. The nasal and conjunctival samples of the dogs were tested for CDV-Ag using a rapid test (Bioguard Corporation®, Taiwan) by the manufacturer's protocol. To rule out diseases that could cause symptoms similar to CDV, fecal swabs were collected and tested for Canine Coronavirus and Canine Parvovirus antigens (Asan Easy Test CCV/CPV®, ASAN Pharm. Co., Korea) following the procedure.

Zonulin analyses were performed on the frozen plasma samples using ELISA test kits after thawing them at room temperature, following the manufacturer's instructions. The ELISA kit was left at room temperature for 30 minutes. The concentrated wash solution was diluted at a ratio of 1:25 and 1.0 ml of diluent was added to the zonulin standard sample, which was then dissolved. Three hundred µL of standard diluent was added to seven tubes and they were mixed; the eighth tube was designated as the negative control. The biotinylated antibody solution and enzyme-conjugate fluid were prepared and diluted as required. Color reagents A and B were mixed. The strips were incubated by adding 100 µL of the sample or zonulin standard to the wells and incubating them at 37°C for 90 minutes. The biotinylated antibody was added and incubated at 37°C for 50 minutes. Enzyme-conjugate fluid was added and incubated at 37°C for 60 minutes. The ELISA plate was washed five times, then 100 µL of color reagent was added and incubated in the dark. When the color deepened, measurements were taken, and absorbance values were read. A standard curve was drawn, and sample concentrations were calculated.

Descriptive statistics and normality tests were performed on the data obtained in the study. Descriptive statistics are presented in the table. The Shapiro-Wilk test determined that the data did not show normal distribution. Although logarithmic transformation processes were applied, the data were still found to be non-normally distributed. Differences between the groups were determined using the Mann-Whitney U test. All analyses were performed using the SPSS 22.0 program and differences were considered significant when the p-value was less than 0.05.

3. Results

3.1. Clinical Findings

The demographic findings of the animal groups included in our study are presented in Table 1. Lethargy and ocular discharge were observed in 10 cases out of 20 in the patient group, while nasal discharge and coughing were noted in 9 cases. Eight dogs exhibited symptoms of dyspnea and anorexia and vomiting and diarrhea were observed in 5 dogs. Myoclonus was present in all cases. It was determined that lethargy and ocular discharge (n=10) were the most commonly observed clinical signs. Vomiting and diarrhea (n=5) were found to be less frequent compared to other clinical findings.

Table 1. Demographic data of infected and healthy dogs.

Patient Number	Age	Breed	Gender	Healty Number	Age	Breed	Gender
1	3	Mixed	Female	**1**	3	Mixed	Male
2	1	Mixed	Male	**2**	3	Mixed	Female
3	1	Mixed	Male	**3**	2	French Bulldog	Male
4	2	Mixed	Female	**4**	5	Golden Retriever	Male
5	1	Mixed	Male	**5**	4	Labrador Retriever	Female
6	4	Mixed	Female	**6**	3	Labrador Retriever	Female
7	2	Mixed	Male	**7**	7	Mixed	Female
8	2	Mixed	Female	**8**	8	Mixed	Male
9	1	Mixed	Female	**9**	1,5	Mixed	Male
10	2	Mixed	Female	**10**	3	Pomeranian	Male
11	3	Mixed	Male				
12	1	Mixed	Female				
13	6	Mixed	Female				
14	4	Mixed	Male				
15	4	Mixed	Female				
16	1	Mixed	Female				
17	1	Mixed	Male				
18	1	Mixed	Male				
19	1	Mixed	Female				
20	2	Mixed	Male				

3.2. Hematological Findings

The hematological parameters considered in the study are presented in Table 2. It was observed that the WBC counts of the infected dogs were significantly higher ($p=0.01$) than those in the healthy group, although this increase was not significant in NEU and LYM. RBC, HCT and HGB levels were statistically significantly higher ($p<0.05$) in the healthy dogs compared to the infected dogs. In parallel with these parameters, MCH and MCHC levels were also significantly higher ($p=0.024$) in healthy dogs compared to the infected ones. It was determined that the changes in platelet and platelet indices did not show any statistically significant differences.

Table 2. The average hematological values of the infected and healthy dogs.

Parameter	Infected $\bar{X} \pm SH$	Healthy $\bar{X} \pm SH$	*P value*
WBC (10^9)/L	16,80 ± 1,69	10,27 ± 0,95	**0,01**
NEU (10^9)/L	4,70 ± 1,06	2,10 ± 0,17	0,155
LYM (10^9)/L	0,57 ± 0,09	0,40 ± 0,07	0,286
MON (10^9)/L	11,23 ± 1,40	6,83 ± 0,53	**0,049**
EOS (10^9)/L	0,20 ± 0,04	0,08 ± 0,01	0,422
BAS (10^9/L)	0,05 ± 0,01	0,03 ± 0,004	0,948
RBC (10^{12})/L	6,47 ± 0,36	7,98 ± 0,29	**0,022**
HGB (g/dL)	12,82 ± 0,57	18,03 ± 0,46	**0,001**
HCT (%)	43,83 ± 2,58	54,00 ± 1,96	**0,017**
MCV (fl)	67,47 ± 0,87	68,00 ± 2,37	0,914
MCH (pg)	20,18 ± 0,43	22,89 ± 1,11	**0,024**
MCHC (g/dL)	29,97 ± 0,71	33,71 ± 1,37	**0,024**
PLT (10^9)/L	322,86 ± 30,34	302,70 ± 37,40	0,681
MPV (fl)	9,86 ± 0,26	9,78 ± 0,48	0,475
PCT (%)	0,30 ± 0,02	0,29 ± 0,03	0,619

3.3. Zonulin Levels

When plasma zonulin levels were examined, it was found that the zonulin levels of infected dogs were significantly higher (p=0.001) compared to healthy dogs (Figure 1). The mean plasma zonulin level in infected dogs was 22.6 ± 1.38 ng/mL, while the plasma zonulin levels in the healthy control group were 2.06 ± 0.41 ng/mL (Table 3).

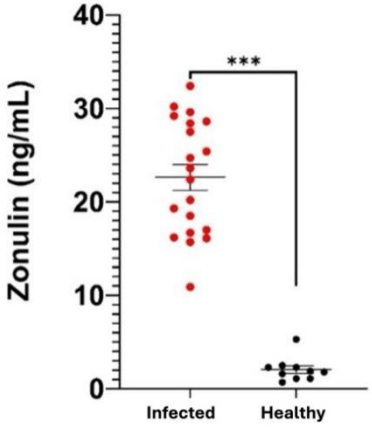

Figure 1. Plasma zonulin levels in infected and healthy dogs.

Table 3. Plasma zonulin levels in infected and healthy dogs.

Parameter		Infected	Healthy
Zonulin (ng/mL)	**Average**	22,6	2,06
	Standard Error	1,38	0,41
	CI (%95)	19,7 - 25,5	1,14 - 2,98
	P Value	0,001	

4. Discussion

Canine distemper virus is an agent that can manifest with systemic symptoms related to the gastrointestinal and/or respiratory systems, along with central nervous system involvement (15,16). Clinical findings include anorexia, fever, nasal/ocular discharge, coughing, dyspnea, vomiting and diarrhea (17,18). These findings can occur in combination and neurological symptoms may appear without systemic signs (16,19). In our study, clinical signs such as myoclonus, lethargy, vomiting, diarrhea, coughing, dyspnea and ocular and nasal discharge were evaluated. Respiratory system signs, particularly nasal discharge, ocular discharge, coughing and dyspnea, were identified as the dominant clinical signs (20,21). Lethargy and ocular discharge were observed in 50% of the dogs, while respiratory symptoms were present in 9/20 and 8/20 cases, respectively. Gastrointestinal signs were seen in 20% of the cases. While neurological signs were present in all infected dogs, no signs such as circling or tetraplegia were observed. The symptoms encountered were found to be consistent with previous studies (22, 23,24,25,26). While the agent leads to the loss of B and T cells, Buragohain (2017) reported that WBC and lymphocyte counts were within the normal range (27). Other studies have shown a significant decrease in monocyte counts and an increase in granulocytes in dogs infected with CDV, which has been associated with secondary bacterial infections and inflammatory reactions (28,29,30). In our study, it was determined that the WBC values of infected dogs were higher than those of healthy dogs and these changes could reflect secondary bacterial infections. Additionally, high antibody levels and clinical findings suggest that the disease is complicated by secondary infections, which are associated with prolonged cases (31). In our study, the red blood cell parameters of dogs infected with CDV were found to be significantly lower compared to healthy dogs. Studies have reported that CDV causes anemia in infected animals due to bone marrow suppression and the depression of progenitor cells (27,32,33). The decrease in MCH and MCHC values reflects microcytic hypochromic anemia and these findings are consistent with the results obtained by Headly and Sukura (2009) and Buragohain (2017) (27,34). The effects of the canine distemper virus on the central nervous system are often associated with neurological disorders and a poor prognosis. Neurological signs can appear without other systemic symptoms, with the virus primarily targeting the myelin tissues in the brain and spinal cord. Demyelination typically occurs three weeks after the onset of infection, but it can manifest earlier in cases without immunosuppression or inflammation (35,36). Due to its affinity for lymphoid tissues, the virus enters the body through various pathways, including the gastrointestinal system and may influence neurological symptoms depending on the host condition. Gastrointestinal changes affect gut permeability, microflora and the enteric nervous system (37,38,39). Alterations in the gut microbiota facilitate communication between the enteric and central nervous systems, maintaining the integrity of body barriers (40,41,42).

The permeability of the blood-brain barrier is used as a mechanism of damage by many viruses (43,44). This barrier is regulated by glial cells and is sensitive to external stimuli (45). Disruption of the blood-brain barrier leads to neurological diseases and infections of brain tissue (46,47). Microbial translocation and gut dysbiosis have been associated with viral infections and COVID-19 (48,49). It has been reported that zonulin levels are lower in patients with COVID-19 compared to those who have recovered. Additionally, zonulin has been closely associated with the breakdown of the blood-brain barrier in patients with multiple sclerosis and was found to be related to gut permeability and disease severity (3). An interesting possibility is that zonulin may have a systemic effect on epithelial barriers other than the intestinal barrier. An *in-vitro* study demonstrated that zonulin could increase the permeability of both the intestinal and blood-brain barriers through similar mechanisms (50) and in a rodent model, zonulin was found to increase the permeability of the blood-lung barrier *in-vivo* (11). Similarly, studies conducted in diarrheic dogs, including those with distemper, have shown increased plasma/serum zonulin levels (39,51,52). In line with these findings, our study also found significantly elevated zonulin levels in distemper-positive dogs (22.6 ± 1.38 ng/mL) characterized by neurological signs compared to healthy dogs (2.06 ± 0.41 ng/mL) ($p=0.001$).

Conclusion

It was observed that zonulin, a tight junction regulator, could be a sensitive marker of increased intestinal and blood-brain barrier permeability and it might play a significant role in mediating the gut-brain axis in the pathogenesis of neuroinflammatory canine distemper virus (CDV) disease in dogs. Future studies should not only focus on serum zonulin levels but also include cerebrospinal fluid (CSF) sampling to monitor both plasma and CSF zonulin levels, which could

contribute to understanding the mucosal barrier-related pathophysiological processes of the disease.

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