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Epidemiological Observation on Recent Outbreaks of Canine Distemper in Korea

Doo Kim[1], Ji-young Park, So-jeo Ahn, Seok-young Jeoung and Son-il Pak

Department of Veterinary Medicine, Kangwon National University, Chunchon 200-701, Korea

Abstract : To characterize the recent outbreaks of canine distemper (CD) in Korea, we carried out epidemiological investigations by clinical observations, serum neutralizing (SN) antibody titer determination and RT-PCR on the 315 dogs which were clinically suspected as canine distemper virus (CDV) infection. One hundred and sixty two of 315 dogs were infected with CDV. Breed or gender did not seem to have effects on the prevalence of CD. The major part of dogs were in young age from 6 weeks to 18 weeks of age, and were not vaccinated or incompletely vaccinated. Clinical signs of dogs with CD were multisystemic and extremely variable. Dogs died from CD had significantly more ocular signs and neurologic signs than those of dogs survived ($p<0.05$). The SN titers against CDV of 157 (96.9%) dogs were under 1:16, which is less than protective level. One possible explanation for recent outbreaks of CD in Korea might be low antibody titers against CDV because of vaccination failure. Therefore, to reduce the impact of virulent infection in the dog population, dogs should be vaccinated adequately and prophylactic measures should include isolation of young dogs from the dog population until vaccination can be expected to provide protection.

Key words **:** Canine distemper, epidemiology, Korea.

Introduction

Canine distemper (CD) is a highly contagious, acute or subacute systemic viral disease caused by canine distemper virus (CDV) classified into the Morbillivirus genus of the Paramyxoviridae. There is only one serotype of virus, but strains vary in virulence[2,9].

The host spectrum of CDV comprises dogs, many other carnivores and noncarnivores as well as marine mammals[6,21,24,29]. CD is the commonest in unvaccinated dogs in urban areas. Nonimmunized dogs of any age are susceptible, but most cases occur between 2 and 6 months of age as puppies that have lost maternal antibody start to be allowed out and encounter infection[19,20,25]. Potential for clinical illness varies depending on the age of the infected dog and the strain of the virus. The clinical course of acute CD is affected by the extent of secondary bacterial infection, but this factor does not affect the diseases of central nervous system[9].

The modified live CDV vaccines are currently used for prophylaxis, and considered to be effective in controlling CD[7]. However, in 1990s, outbreaks of CD has been reported in Korea as well as other countries including Denmark, Finland, and Japan, even though modified live CDV vaccines were used as the same way as before[4,8,11,18,30]. A previous study on dogs that succumbed to the CD in spite of vaccination suggested that a critical decline in population immunity had contributed to the severity of the outbreak[8]. Although level of neutralizing antibodies alone does not predict the protection of an individual against infection, the average level of neutralizing antibodies in population satisfactorily indicates the immune status of the population[12].

In this study, recent outbreaks of CDV infection in Korea were investigated on the basis of clinical signs, vaccination status and immunological status of infected dogs. And the background factors involved outbreaks of CD were assessed to characterize the recent outbreaks of CD.

Materials and Methods

Clinical specimens and data collection

Samples of peripheral blood and/or conjunctiva epithelial cells from 315 dogs which were clinically suspected for CDV infection were collected by local veterinarians in Kangwon, Seoul, and Kyunggi areas between February, 2002 and October, 2002. Details on the gender, breed, age, clinical signs, vaccination status, and prognosis on 315 dogs were recorded.

Vaccination status was recorded according to the notification by owner of the patient and was divided into three categories; complete vaccination (primary course administered and booster vaccinations given every year within a month of the due date), incomplete vaccination (less than three times vaccination were administered in primary course vaccination), and none vaccination.

Clinical signs were characterized as respiratory, gastrointestinal, ocular and neurologic signs. Respiratory signs included bronchitis, sometimes pneumonia, and other relatively mild signs including coughing and nasal discharge. Gastrointestinal signs included vomiting and diarrhea. Ocular signs included mild or mucopurulent discharge with intensely congested conjunctivae and sclerae. Neurologic signs were behavior changes, local myoclony, tonic-clonic spasms, seizures, convulsion, ataxia, coma, circling, and paresis. Prognosis was recorded according to the notification by responsible veteri-

[1]Corresponding author.
E-mail : kimdoo@kangwon.ac.kr

narians of the patient dogs.

Reverse transcription-polymerase chain reaction (RT-PCR)

The RT-PCR was carried out with a minor modification of the protocol by Frisk *et al*[10] to detect CDV neucleoprotein (NP) gene from canine peripheral blood mononuclear cells (PBMCs) and/or from conjunctival swab samples. Total RNA was extracted from each sample with the E.Z.N.A® Blood RNA Kit (Omega Biotex, Inc., GA) according to manufacturer's instruction. Oligonucleotide primers used for amplification of the CDV NP gene sequences were selected from the reference[10]. One sense primer was a 21-mer (5'-ACAGGAT-TGCTGAGGACCTAT-3') and the other antisense primer was a 21-mer (5'-CAAGATAACCATGTACGGTGC-3'), located at positions 769-789 and 1,035-1,055 nucleotides, respectively. Positions are indicated according to the positions of Sidhu *et al*[26], which are available from GenBank-EMBL data bank under accession No. AF014953. The expected amplicon length by the primer pair was 287-bp. For synthesis of cDNA, RT was performed at 45°C for 2 hour with 200 U of Moloney murine leukemia virus reverse transcriptase (GIBCO BRL, Gaithersburg, MD) and 100 pM of antisense primer. After inactivation of the murine leukemia virus reverse transcriptase, the PCR master mixture (100 pM of each CDV oligonucleotide primer, sense and antisense primers) was added, followed by denaturation at 94°C for 1 min and 35 cycles consisting of denaturation at 94°C for 1 min, annealing at 41 °C for 1 min and extention at 72°C for 1 min, and final extention at 72°C for 5 min in a thermocycler (GeneAmp PCR System 9600, Perkin Elmer Corporation, Norwalk, CT). The PCR products were analyzed on a 2% agarose gel after staining with ethidium bromide.

Serum samples and antibody measurement

The presence of serum neutralizing (SN) antibodies was measured with modification of the microneutralization test described by Appel and Robson[3]. Briefly, two fold serum dilutions of 50 μl were prepared (starting dilution, 1:2 in minimum essential medium, 1/4, 1/8, 1/16, 1/32, 1/64. 1/128, 1/256, 1/512 and 1/1024). A total of 50 μl of the minimum essential medium with 200 median tissue culture infective dose of the Ledler strain was added to each well. And then, plate was incubated at 37°C for one hour. A total of 100 μl of the Vero cell suspension (1×10^5cells/well) was added to each well, and the titration plates were incubated at 37°C in 5% CO_2 for 3 to 5 days. The neutralizing capacity of the sera was determined by inhibition of the Ledler-CDV-induced cytopathogic effect (giant cell formation).

Statistical analysis

Data from the whole population were summarized by calculating descriptive statistics. The potential association of age, signs, vaccination and SN titer was evaluated by logistic regression (live = 1, death = 0) by creating n-1 dummy variables for variables with n levels. All independent variables initially were screened by univariate analysis to assess simple association between dependent and independent variables by calculating odds ratio (ORs), associated 95% confidence intervals (95% CI), and *P* values. Variables that met a critical *P* value of less than 0.1 in the univariate analysis were included in the multivariate logistic regression analysis. Selection of variables for multivariable modeling with a forward stepwise analysis were performed as described by Hosmer and Lemeshow[16]. The multivariate modeling allow to evaluate several factors simultaneously while controlling for potential confounding factors. Parameter estimates and adjusted ORs were estimated from the final multivariale logistic model. The Hosmer-Lemeshow statistic was calculated for the final models to evaluate the goodness-of-fit of the data. Differences in mean SN titer between categorized groups were compared by using Studednt's *t*-test or one-way analysis of variance. All of the analyses described above were performed using SAS version 8.1 (SAS Institute, Cary, NC). *P* values less than 0.05 were considered significant, if not indicated otherwise.

Results

Distribution of the dogs with CD in epidemiological parameters

Among the total of 315 dogs that were clinically suspected for CDV infection, 162 dogs were diagnosed as CD positive by RT-PCR. Of these 162 dogs with CD, female dogs (86 dogs, 53.1%) were more than male dogs (76 dogs, 46.9%). The distribution of the dogs with CD according to age was shown in Fig 1. Five (3.1%) of 162 dogs were less than 6 weeks of age, 127 (78.4%) dogs were between 6 and 18 weeks of age, 13 (8.0%) dogs were between 18 and 52 weeks of age, and 17 (10.5%) dogs were over 52 weeks of age. The most prevalent breed was Cocker Spaniel (14.2%), and then the prevalence was lowered in Shihtzu (12.3%), followed by mixed breed (11.1%), Miniature Schnauzer (7.4%), Pekingese

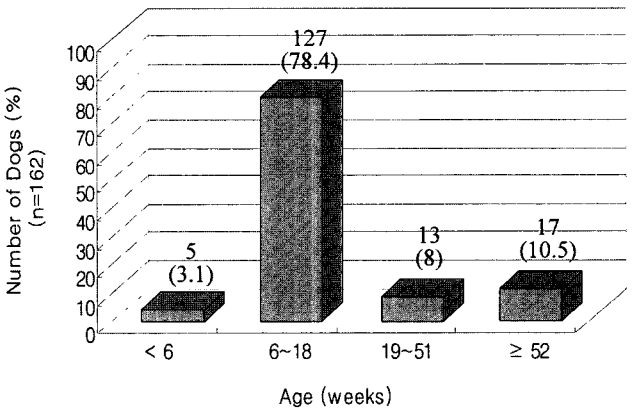

Fig 1. Distribution of the dogs with canine distemper according to age (n=162). The majority of the dogs were included in age group from 6 to 18 weeks.

Table 1. Distribution of the dogs with canine distemper according to breeds (n=162)

Breed*	No. of dogs	%	Breed	No. of dogs	%
Cocker Spaniel	23	14.2	Bulldog	2	1.2
Shihtzu	20	12.3	Pug	2	1.2
Mixed	18	11.1	Rottweiler	2	1.2
Miniature Schnauzer	12	7.4	Saint Bernard	2	1.2
Pekingese	11	6.8	Chinese Crested dog	1	0.6
Yorkshire Terrier	11	6.8	Tosa	1	0.6
Poodle	6	3.7	Sharpei	1	0.6
Retriever	6	3.7	Vizsla	1	0.6
Maltess	6	3.7	Dachshund	1	0.6
Jindo	5	3.1	Collie	1	0.6
Alaskan Malamutt	5	3.1	Chin	1	0.6
Siberian Husky	5	3.1	Chow Chow	1	0.6
Beagle	5	3.1	German Shepherd	1	0.6
Pomeranian	4	2.5	Chihuahua	1	0.6
Basset Hound	3	1.9	Samoyed	1	0.6
Miniature Pinscher	3	1.9			

*The total 31 breeds were included.

(6.8%), Yorkshire Terrier (6.8%) (Table 1).

One hundred and thirty five (83.3%) dogs of 162 dogs showed respiratory signs with other signs (gastrointestinal, ocular or neurologic signs), 78 (48.2%) dogs showed gastrointestinal signs with other signs, 88 (53.1%) dogs showed ocular signs with other signs and 40 (24.7%) dogs showed neurologic signs with other signs. The twenty three of the 162 (14.2%) dogs showed only respiratory signs, 4 (3.1%) dogs showed only gastrointestinal signs, 2 (1.2%) dogs showed only ocular signs, and 4 (1.2%) dogs showed only neurologic sings (Fig 2).

Vaccination histories were shown in Fig 3. Seventy eight (48.2%) of 162 dogs were none vaccination status, 59 (36.4%) dogs were incomplete vaccination status, and 11 (6.8%) dogs were complete vaccination status. However, 14 (8.6%) dogs were unknown about the vaccination history.

In distribution of the dogs with CD according to SN titer (Fig 4), 53 (32.7%) of 162 dogs had undectable antibody titer (less than 1:2), 24 (14.8%) of the 162 dogs had titer 1:2, 45 (27.8%) dogs had titer 1:4, 35 (21.6%) dogs had titer 1:8 and only 5 (3.1%) dogs had titer $\geq$:16. One hundred and fifty seven (96.9%) dogs with CD had titer $<$1:16 which is a less than protective level.

At the end of the study, 44 dogs (27.2%) were survived, 77 (47.5%) dogs were died, however, 41 (25.3%) dogs were not known about the prognosis.

Comparison of SN titers according to CDV infection, prognosis, age, and vaccination status

The SN titers of CD negative (n = 153) dogs were significantly higher, compared to those of dogs with CD (n = 162) (Table 2; $P<0.05$). There was no significant difference in the

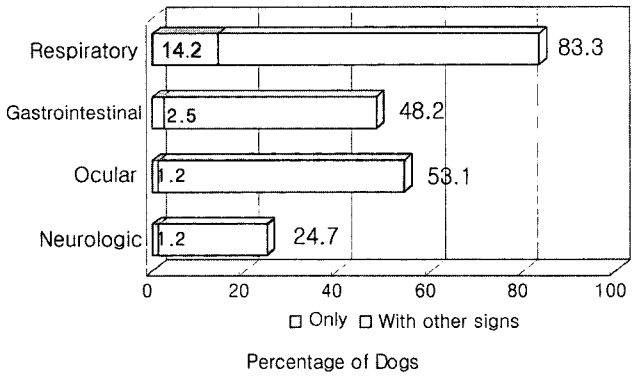

Fig 2. Distribution of the dogs with canine distemper according to clinical signs (n=162). Black parts of bars representing only one clinical sign and white parts representing more than 2 clinical signs.

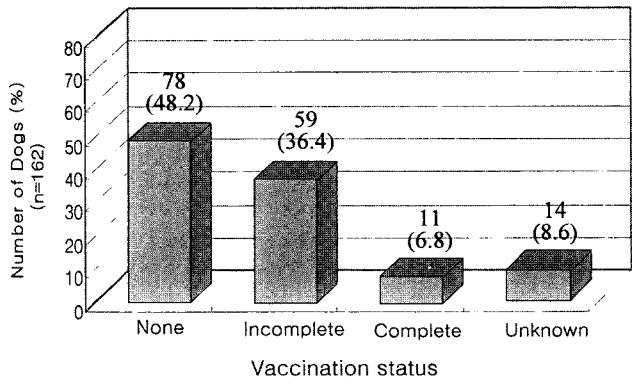

Fig 3. Distribution of the dogs with canine distemper according to vaccination status (n=162). The major part of dogs were included in none and incomplete vaccinated groups.

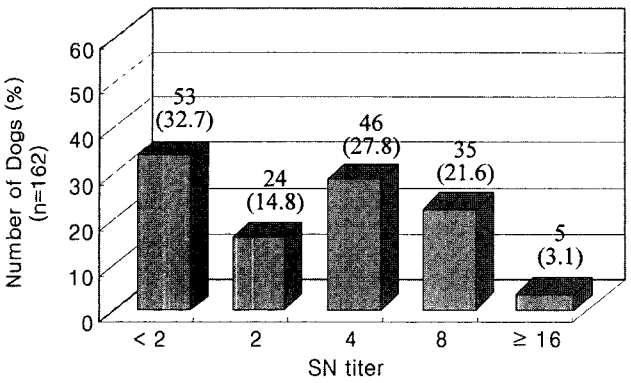

Fig. 4. Distribution of the dogs with canine distemper according to serum neutralizing titer (n=162).

Table 2. Comparison of SN titers according to CDV infection

CDV infection	n	Mean± SD	*P*
Positive	162	10.6± 3.9	0.0045
Negative	153	20.4± 5.6	

Table 3. Comparison of SN titers according to prognosis

Prognosis	n	Mean± SD	*P*
Survived	44	13.6± 3.3	0.1319
Died	77	7.6± 4.6	

SN titer between 44 survived dogs and 77 died dogs with CD ($P > 0.05$). However, titers in the survived dogs were a little bit higher than those of died dogs (Table 3). The dogs above one year old had significantly higher SN titers, compared to dogs aged 6 to 51 weeks ($P < 0.05$), but no difference in comparison with dogs under 6 weeks and more than 1 year ($P > 0.05$, Table 4). The none vaccinated dogs showed lower titer than the incomplete vaccinated dogs ($P < 0.05$), with the lowest titer in the complete vaccinated dogs (Table 5).

Table 4. Comparison of SN titers according to age

Age (weeks)	n	Mean± SD	*P*
< 6	5	6.8± 3.8	0.0659
6 - 18	127	9.6± 3.2	0.0035
19 - 51	13	5.6± 2.1	0.0052
≥ 52	17	42.8± 7.3	Reference

Table 5. Comparison of mean SN titers according to vaccination status

Vaccination status	n	Mean± SD	*P*
Complete	11	6.6± 2.7	0.6812
Incomplete	59	16.2± 5	0.0325
None	78	7.6± 3.1	Reference

Univariate analysis

Table 6 showed unconditional logistic regression analysis of the relationship between study variables and the outcome by CDV infection. A percentage of dogs with ocular signs that survived (24.2%, 16/66) was significantly ($P=0.0028$) smaller than a percentage of dogs that did not have the ocular signs

Table 6. Unconditional logistic regression analysis of the relationship between study variables and the outcome by canine distemper virus infection

Variable		No. survived / No. cases	OR* (95% CI)	*P*
Sex	Male	23 / 57	1	
	Female	21 / 64	0.7 (0.3-1.5)	0.3902
Age group	<6	3 / 4	3.8 (0.3-51.4)	0.3069
	6-18	34 / 98	0.7 (0.2-2.6)	0.8747
	19-51	3 / 10	0.5 (0.1-3.5)	0.7269
	≥ 52	4 / 9	1	
vaccination status	None	22 / 55	1	
	incomplete	14 / 47	0.6 (0.3-1.4)	0.028
	complete	3 / 7	1.1 (0.2-5.4)	0.8846
Respiratory signs	Yes	37 / 104	1	
	No	7 / 17	1.3 (0.4-3.6)	0.6568
Gastrointestinal signs	Yes	20 / 60	1	
	No	24 / 61	1.3 (0.6-2.7)	0.4923
Ocular signs	Yes	16 / 66	1	
	No	28 / 55	3.2 (1.5-7.0)	0.0028
Neurologic signs	Yes	7 / 30	1	
	No	37 / 91	2.2 (0.9-5.8)	0.0919

*The 95% confidence interval of the odd ratio was calculated as the antilog (coefficient ± 1.96 × SE of the coefficient).

Table 7. Odd ratios (ORs) and 95% confidence intervals (CIs) of predictor variables associated with the outcome by CD virus infection in the final logistic regression model

Variable		No. survived / No. cases	OR (95% CI)	*P*
Ocular sign	Yes	16 / 66	1	
	No	28 / 55	3.1 (1.4-6.8)	0.0042
Neurologic sign	Yes	7 / 30	1	
	No	37 / 91	2.1 (0.8-5.5)	0.1432

(50.9%, 28/55). The percentage of dogs with neurologic signs that survived (23.3%, 7/30) was significantly ($P=0.0919$) smaller than the percentage of dogs that did not have the neurologic signs (40.7%, 37/91). None of the other variables were significantly associated with survival; sex, age, group, vaccination status, SN titer, respiratory signs, and gastrointestinal signs. Although not significant, a percentage of dogs with respiratory signs that survived (35.6%, 37/104) was smaller than percentage of dogs without respiratory signs that survived (41.2%, 7/17). Dogs with gastrointestinal signs also were noted to have a lower survival rate (33.3%, 20/60) than dogs that did not have gastrointestinal signs (39.3%, 24/61), but this difference was not significant.

Multivariate analysis

The final multivariate model included the variables of ocular signs and neurologic signs (Table 7). A percentage of dogs with ocular signs that survived (24.2%, 16/66) was significantly ($P=0.0042$) smaller than percentage of dogs that did not have ocular signs (50.9%, 28/55). Unlikely in the univariate analysis, neurologic signs was no longer significantly associated with survival.

Discussion

For several decades, CD had been controlled successfully by the use of attenuated CDV live vaccines. However, recently a lot of outbreaks of CD were reported throughout the world in spite of intensive vaccination[5,14,15,17,23]. Although various commercial vaccines also have been used to prevent CD in Korea, outbreaks of CD were continued[18,30]. Such problems may arise from the following reasons. One possible explanation for recent outbreaks of CD in Korea may be low CDV antibody titers from failure of vaccination. Second, despite dogs received the vaccines, antibody titers against CDV did not raised. Here may also be problems with improper handling of the vaccine and with the vaccination schedule, for instance, vaccinating puppies still possessing maternal antibodies which may interfere with the generation of immunity. Third, it is occasionally assumed that commercial vaccines in use would not protect properly aganist current field virus infections even if applied correctly[13,17].

In this study, 84.6% of the dogs with CD were none or incomplete vaccination status. Thus, it was considered that recent outbreak of CD in Korea might be caused by the failure of vaccination and/or by the inadequate antibody responses to CDV vaccines. And the 96.9% of dogs with CD had SN titer against CDV $<1:16$ that is less than protective titer level. Therefore, one possible explanation for recent outbreaks of CD in Korea might be ascribed to low antibody titers from failure of vaccination. However, 3.1% of the dogs with CD had titer $\geq 1:16$ that is more than protective titer level. These dogs may have been infected with field CDV strain(s) containing genetic variant responsible for the outbreak[4,8,14]. An *et al*[1] analyzed nucleotide sequences of the NP gene of CDV isolated from dogs and a badger in Korea and compared with vaccine strains. And they were reported that nucleotide sequences of CDV NP gene isolated from clinical samples differ from vaccine strains.

In comparison of the mean SN titers according to the vaccination status in this study, the titer of the none vaccinated dogs were significantly lower than those of the incomplete vaccinated dogs. However, the complete vaccinated dogs had the lowest titer. These results would be caused by the interference with maternal antibodies or improper handling of the vaccine[22,28]. In concert, the most important epidemiological trend of the data from the present CD outbreak is that unvaccinated individuals and laxity in vaccination procedures of the individual animals seem to account for the majority of the confirmed clinical CD cases.

Most cases of CD usually occur between 2 and 6 months of age as puppies have lost their maternal antibody and started to be allowed out and encounter infection[20]. In this study, dogs with CD had the various age range from 2 weeks to 8 years old, however, majority (78.4%) of dogs were aged from 6 to 18 weeks of age in which was a period for vaccination.

A tentative diagnosis of CD can be conducted based on typical clinical signs in young dogs[25], however, this is not fully supported. So, the various laboratory diagnostic techniques are needed for final diagnosis. In this study, detection of CDV infection was achieved using the RT-PCR with a set of NP gene specific primers. The authors determined the presence of the NP gene in 162 (51.4%) of the 315 clinically CD suspected dogs. And this detection rate was similar to the other study[27]. The possibility of detecting vaccine virus from the clinical specimens is hardly considered, because the vaccine strain of CDV developed no clinical symptoms after the inoculation in the SPF puppy[27].

Clinical signs of dogs with CD in this study were multisystemic. Most of dogs had two or three clinical categories, and the respiratory signs were the most prevalent clinical signs. Dogs with ocular and neurologic signs were significantly associated with decreased survival in univariate analysis ($P<0.05$). These results may relate to pathophysiology of CD that affected dogs with CD may have poor cell-mediated immunity, viral spread and multiplication is unchecked and extensive growth in epithelia results in classical 'catarrhal' CD with respiratory, gastrointestinal and ocular signs from 2 weeks postinfection onwards[12,25]. Dogs with severe catarrhal CD are

also likely to develop neurologic signs from 4 weeks postinfection onwards[20]. However, this study showed that neurologic signs were not associated with the survival in multivariate analysis. It was considered that this result might be due to the small number of animals survived in each group (7 vs 37, respectively). And due to limitations in numbers of dogs and lack of support for a multicenter study, the authors did not attempt to validate this model using another population of dogs.

This study showed that the recent outbreaks of CD in Korea might be ascribed to low antibody titers from failure of vaccination. And because the contribution of a vaccine to the immunity of the population depends on more critical vaccination, the adequacy of vaccination policy and the efficacy of vaccines should be reviewed periodically to maintain the population immunity at an adequate level[4,7,8]. It is impossible to eradicate CDV essentially because of the reservoir in population. Thus, a more extensive use of CDV vaccines should be encouraged in order to reduce the impact of virulent infections in the dog population. Furthermore, as no immunization strategy can eliminate the protective gap between passive maternal immunity and actively acquired immunity, prophylactic measures should include isolation of young dogs from the dog population until vaccination can be expected to provide protection.

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최근 국내발병 개 디스템퍼에 대한 역학적 조사

김 두[1] · 박지영 · 안소저 · 정석영 · 박선일

강원대학교 수의학과

요 약 : 본 연구에서는 최근 국내에서 발병하는 개 디스템퍼(CD)의 역학적 조사를 위하여 2002년 2월부터 2002년 10월까지 강원도, 경기도와 서울특별시의 10개 동물병원 수의사에 의하여 CD에 감염된 것으로 잠정진단된 315마리의 개를 대상으로 하였다. 개체의 신상자료와 임상증상을 조사하였으며 CD를 확진하기 위하여 혈액의 단핵구나 결막 상피세포에서 CDV의 NP gene을 RT-PCR로 증폭하였다. CD로 의심되는 총 315마리 중 162마리가 CD 양성으로 진단되었으며 성별과 종에 따른 발병율에는 차이가 없었다. 나이별 분포는 백신을 접종해야 하는 기간인 6-18주에 가장 높은 분포를 보였으며 1세 이상에서도 소수 발병하였다. CD 환축은 호흡기 증상, 위장관 증상, 눈의 증상 등 다양한 증상이 나타나 임상증상에 근거하여 CD를 진단하기에 어려움이 있었다. CD 양성의 개 중 84.6%가 백신을 한번도 맞지 않았거나 예방접종을 제대로 실시되지 않은 상태였으며 CDV에 대한 혈청 중화 항체가는 96.9%의 개가 방어수준 이하인 1:16 이하를 나타내었다. CD 양성 162 마리와 CD 음성으로 진단 된 153마리의 혈청 중화 항체가 사이에는 통계적인 유의차가 인정되었으며 ($P < 0.05$), CD 양성 개 중에 생존 한 개들은 폐사한 개들보다 중화 항체가 높은 경향을 보였다. 눈의 증상과 신경증상을 보인 개체들은 다른 개체들에 비해 생존율이 유의하게 낮은 것으로 나타났다 ($P < 0.05$). 본 연구의 결과 현재 국내에서 발병하고 있는 개 디스템퍼는 예방접종의 실패에 따라 개들의 항체 수준이 전반적으로 낮은 것에 기인하는 것으로 판단되므로 예방접종에 대한 전반적인 검토가 필요하며 예방을 위하여 감염에 취약한 시기에는 감염원에 접촉을 최소화하는 것이 중요할 것으로 판단되었다.

주요어 : 개 디스템퍼, 역학, 대한민국