CLINIC AND SURGERY

Epizootiology of canine distemper in naturally infected dogs in Goiânia, Brazil

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ABSTRACT: Although the epizootiological profile of canine distemper in Goiânia is unknown, there is clinical evidence for a high incidence of canine distemper virus (CDV) infection among dogs. Therefore, this study determined the epizootiological characteristics of canine distemper in naturally infected dogs. Data of 46 dogs that tested positive for the CDV based on immunochromatography or reverse transcription-polymerase chain reaction were collected. Data on the sex, breed, age, and vaccination status were obtained from these dogs, and extraneural and neural sign analyses were performed. Although, the infected dogs belonged to both sexes, different breeds, and different age groups, a greater proportion of cases were seen in adults (1–6 years), undefined breeds, and unvaccinated dogs. Among the CDV-positive dogs, 10.87% had been vaccinated. In addition, 4.35% showed neural signs, 8.69% showed extraneural signs, and 86.96% showed both. High lethality was observed, with viral antigen and/or DNA detected in 82.61% dead dogs. Only 8.70% of the total CDV-infected dogs remained alive at the time of their assessment.
Key words: CDV, infectious disease, epidemiology, immunochromatography, RT-PCR.

Epizootiologia da cinomose em cães naturalmente infectados em Goiânia, Brasil

RESUMO: Embora o perfil epizootiológico da cinomose canina em Goiânia seja desconhecido, há evidencia clínica para alta incidência da infecção pelo vírus da cinomose (CDV) nos cães. Este estudo objetivou determinar as características epizootiológicas da cinomose em cães naturalmente infectados. Dados de 46 cães positivos por imunocromatografia ou reação em cadeia da polimerase via transcriptase reversa para o CDV foram coletados. Dados sobre sexo, raça, idade, estado vacinal foram obtidos desses cães, e os sinais extraneurais e neurais foram analisados. Animais de ambos os sexos, diferentes raças e idades foram acometidos. A maior proporção de casos foi vista em adultos (de um a seis anos), sem raça definida e não vacinados. Dentre os cães positivos, 10,87% haviam sido vacinados. Em adição, 4,35% apresentaram sinais neurais, 8,69% sinais extraneurais e 86,96% mostraram ambos. Alta letalidade foi observada, com o antígeno viral e/ou DNA identificado em 82,61% dos cães que foram a óbito. Apenas 8,7% dos cães infectados permaneceram vivos até o momento da avaliação.
Palavras-chave: CDV, doença infecciosa, epidemiologia, imunocromatografia, RT-PCR.

INTRODUCTION

Canine distemper virus (CDV) is the etiological agent of canine distemper, one of the most prevalent infectious diseases in domestic dogs and wild carnivores (MARTINEZ-GUTIERREZ & RUIZ-SAENZ, 2016). It is an cause of death and euthanasia in young and adult dogs of any breed, particularly those with an incomplete vaccination status (FIGHERA et al., 2008; TRAPP et al., 2010; HEADLEY et al., 2012; MARTINS et al., 2020). Infection mainly occurs through inhalation of infectious particles or direct contact with infectious secretions. The CDV can proliferate and spread to different organ systems, including the respiratory, ocular, gastrointestinal, dermatological, and neurological systems (GREENE & VANDEVELDE, 2012).

The diagnosis of canine distemper is essential not only for a therapeutic approach but also for isolating infected dogs. Laboratory tests have been used to present the epidemiological profile of canine distemper in some regions (COSTA et al., 2019; DORJI et al., 2020) using molecular, serological, and histopathological techniques (FRISK et al., 1999; VANDEVELDE & ZURBRIGGEN, 2005; AN et al., 2008; ELIA et al., 2015).

However, the epidemiology of canine distemper in different cities in Brazil, with respect to the positivity rate, analyses of possible risk factors, characterization of multisystemic clinical signs, and improved diagnostic techniques, remains unknown. Therefore, this study provided an epizootiological description of canine distemper in naturally infected dogs in the municipality of Goiânia, Brazil.

MATERIALS AND METHODS

A prospective clinical study was conducted at the Veterinary Hospital of the Veterinary School of the Federal University of Goiás, and the Zoonoses Control Center of Goiânia, Goiás, Brazil, from 2017 to 2020. Reverse transcription-polymerase chain reaction (RT-PCR) or immunochromatographic (IC) analyses were used to detect CDV-positive dogs. Dogs with at least one systemic or neurological sign compatible with a naturally occurring CDV infection were included in the study.

The dogs were divided into three groups based on their clinical signs: extraneural signs (ES), neural signs (NS), and extraneural with neural signs (ENS). Animals in the ES group presented with: hyporexia/anorexia, nasal and/or ocular secretions, dehydration, hyperkeratosis of the foot pads and nose, hyperthermia, diarrhea and/or vomiting, dyspnea and/or coughing and/or pneumonia, enamel hypoplasia, and/or dermal pustules.

Animals in the NS group presented with: changes in mental status (depressed, stuporous, or comatose), motor deficits (ambulatory or non-ambulatory paresis or paralysis/plegia), myoclonus, behavioral changes (aggressiveness, restlessness, dementia, delirium, vocalization, hallucinations, compulsive walking, head pressing, hemi-neglect), seizures, tremors, ataxia (sensory or proprioceptive, cerebellar or vestibular), proprioception deficits, muscle hypotrophy, posture alteration (head tilt, head turn, ventroflexion of the head, opisthotonos, decerebrate and decerebellate rigidity, Schiff-Sherrington kyphosis, lordosis, scoliosis, plantigrade or palmigrade postures), alteration in muscle tone, decreased spinal reflexes, alterations in cranial nerves (like mandibular trismus, strabismus, and nystagmus), and/or paraspinal muscles hyperpathia. Animals included in the ENS group presented with a combination of the signs in both ES and NS groups.

Epizootiological data were collected to describe CDV infections with respect to sex (male or female), age [2–4 months (immune window), 5–11 months (young), 1–6 years (adult), or >7 years (elderly)], breed [undefined breed (UB) or purebred (PB)], and vaccination status (confirmed by a health card vaccine). Dogs that had completed the initial vaccination protocol (3–4 polyvalent vaccines, starting at 6–8 weeks of age, at 21-day intervals, until the animal was 16 weeks old) and the annual booster were classified as having a complete vaccination status. Otherwise, they were considered to have an incomplete vaccination status (DAY et al, 2020). Vaccination information was collected from the Vaccination Record Card of each dog.

Clinical samples (conjunctival swabs, blood, urine, or cerebrospinal fluid) obtained from each animal were tested for CDV antigen using IC (Ag Test kit, Alere, São Paulo, Brazil) or RT-PCR analyses. The IC analysis was performed according to the manufacturer's instructions. Sample extraction was performed using Trizol LS Reagent (Invitrogen, Carlsbad, USA) according to the methodology adapted from FRISK et al. (1999). After extraction, reverse transcription was performed by adding 20 µL of the extracted RNA to 30 µL of a reaction mixture containing 1×, 5× buffer, 4 µL DEPC water, 2 µL random primers (Invitrogen, Carlsbad, USA), 0.4 mM dNTP, 4 mM $MgCl_2$, 20 U/µL RNAsin (Invitrogen, Carlsbad, USA), 200 U/µL M-MLV RT (Invitrogen, Carlsbad, USA), and 0.5 µL DTT. Reverse transcription was performed in an automatic thermocycler (Swift TM Maxi, Esco) for 40 min at 37 °C and then for 10 min at 95 °C.

DNA amplification was performed using the oligonucleotide primers NPp1 sense (5'-ACAGGATTGCTGAGGACCTAT-3' nt 769-789) and NPp2 antisense (5'-CAAGATAACCATGTACGGTGC-3' nt 1055-1035), which target the gene encoding the CDV nucleoprotein (N), amplifying a 287-bp product (FRISK et al., 1999). PCR was performed using 3 µL of the cDNA sample mixed with 22 µL of a mixture comprising 1× GoTaq master mix (Promega, Wisconsin, USA), 0.4 µM NPp1 sense, 0.4 µM NPp2 antisense, and nuclease water-free in a final volume of 25 µL. The microtubes were placed on a T100 Thermal Cycler (Bio-Rad Laboratories, CA, USA) for 5 min at 94 °C, followed by 40 cycles of 1 min at 94 °C, 2 min at 55 °C, 1 min at 72 °C, and 5 min at 72 °C.

PCR products were subjected to electrophoresis on a 1.5% agarose gel (Invitrogen, Foster City, CA, USA) in Tris-borate-EDTA buffer with ethidium bromide (0.1%). Subsequently, the gel was visualized using an ultraviolet light transilluminator (MS Major Science, CA, USA) and the amplified fragments were compared to a DNA ladder (100pb)

(Ludwig Biotec, Alvorada, Rio Grande do Sul). Qualitative variables (epizootiological data and clinical signs) were evaluated using descriptive statistics.

RESULTS

This study included 46 CDV-infected dogs. The CDV-infection frequency in these dogs, with respect to sex, age, breed, and vaccination status, is presented in table 1. In terms of sex, both male and female dogs showed similar infection frequencies. In terms of breed, UB dogs showed high infection frequency at 65.22% (30/46). Among the PB dogs (16/46), most cases were seen in Dachshunds (31.25%, N = 5), followed by Shih Tzu (18.75%, N = 3), Poodle (12.5%, N = 2), Fila Brasileiro (12.5%, N = 2), and miniature Pinscher, Lhasa Apso, Border Collie, and Golden Retriever (6.25% each).

In terms of age, highest infection frequencies were seen in adult (41.30%) and young (30.43%) dogs, while lowest infection frequencies were observed among dogs in the immune window (15.22%) and elderly dogs (10.87%). Lastly, in terms of vaccination status, 10.87% (5/46) of the CDV-infected dogs were vaccinated (Table 2). Among the seven dogs infected during the immune window, only one received two doses of the vaccine, whereas the others were unvaccinated. Approximately 46% (21/46) of the dogs were infected and developed the disease at 2–8 months of age; only one of them was completely vaccinated, whereas the others either incompletely vaccinated or unvaccinated.

With respect to clinical signs, 8.69% (4/46) showed ES, 4.35% (2/46) showed NS, and 86.96% (40/46) showed ENS. Lethality was observed in 82.61% (38/46) of the dogs, of which 34 (89.47%) showed NS and ENS and 4 (10.53%) showed ES. Among the 46 infected dogs, 26.09% (12/46) died naturally, 56.52% (26/46) were euthanized owing to deterioration of their clinical condition, and 8.70% (4/46) were alive at the time of assessment. However, it was not possible to establish whether they were still alive as their owners did not return.

Most of these dogs presented with systemic or multifocal signs of respiratory, gastroenteric, dermatological, or neurological origin, reflecting the proliferation of the virus in different organ systems (Figure 1). In this study, all the dogs showed at least one ES or NS. Several NS were observed, and changes in mentation, motor deficits, myoclonus, behavioral changes, seizures, and tremors were evident (Figure 2).

DISCUSSION

This study showed that CDV infection was responsible for death or euthanasia in 82.61% (38/46) of the dogs, and only 8.70% (4/46) survived. Both male and female dogs, especially those of UB, aged 1–6 years, and with an incomplete vaccination protocol, accounted for the greatest proportion of cases. Among the infected dogs, 10.87% were vaccinated. And 86.96% of the infected dogs showed systemic and neurological signs.

The high lethality observed in this study occurred due to the progression of clinical signs,

Table 1 - Canine distemper virus infection frequency detected by RT-PCR or IC analysis, according to sex, breed, age, and vaccination status, in dogs in the municipality of Goiânia, Brazil (2017–2020).

----------------------------------Variables-----------------------------		Total N	Positive RT-PCR or Immunochromatography (%)
Sex	Male	24	52.17
	Female	22	47.83
Breed	UB	30	65.22
	PB	16	34.78
Age	2–4 months	7	15.22
	5–11 months	14	30.43
	12–72 months (1–6 years)	19	41.30
	>72 months (>7 years)	5	10.87
	NI	1	2.17
Vaccination Status	Complete	5	10.87
	Incomplete	36	78.26
	NI	5	10.87

N, dogs; RT-PCR, reverse transcription-polymerase chain reaction; IC, immunochromatography; UB, undefined breed; PB, purebred; NI, no information.

Table 2 - Canine distemper virus infection detected by RT-PCR or IC analysis, according to sex, breed, age, clinical phase, and state of life in fully vaccinated dogs in the municipality of Goiânia, Brazil (2017–2020).

Sex	Age (months)	Breed	Clinical phase	State of life
Female	5	UB	ES, NS	Dead
Male	12	PB	ES, NS	Euthanized
Male	19	UB	NS	Alive
Female	48	PB	ES, NS	Alive
Male	120	UB	SN	Alive

RT-PCR, reverse transcription-polymerase chain reaction; IC, immunochromatography; UB, undefined breed; PB, purebred; ES, extraneural signs; NS, neural signs.
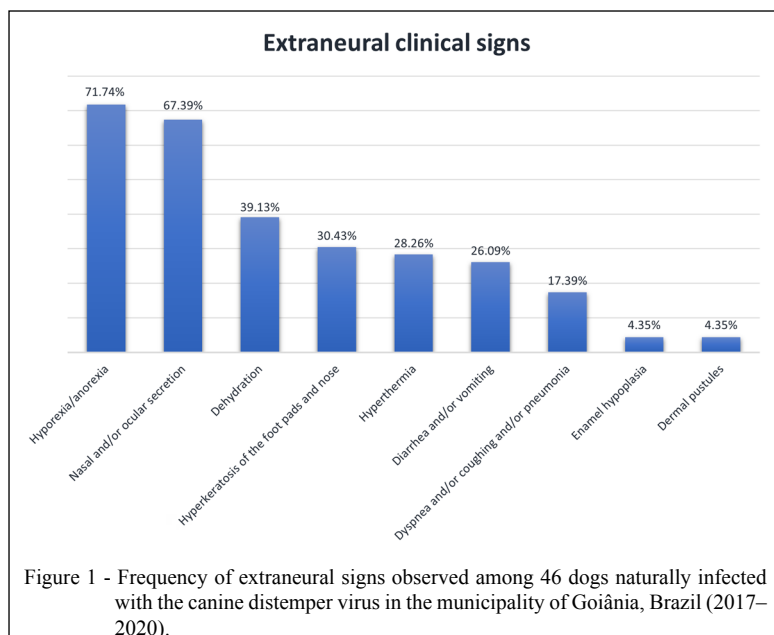
especially neurological, similar to previous study by COSTA et al. (2019) in which 76% (107/141) of CDV-infected dogs died due to systemic and neurological complications. In a study conducted in Australia, 77% lethality was observed in CDV-infected dogs and the clinical presentation was mainly neurological (WYLLIE et al., 2016). These studies showed a correlation between neurological progression and a high rate of death or euthanasia in animals.
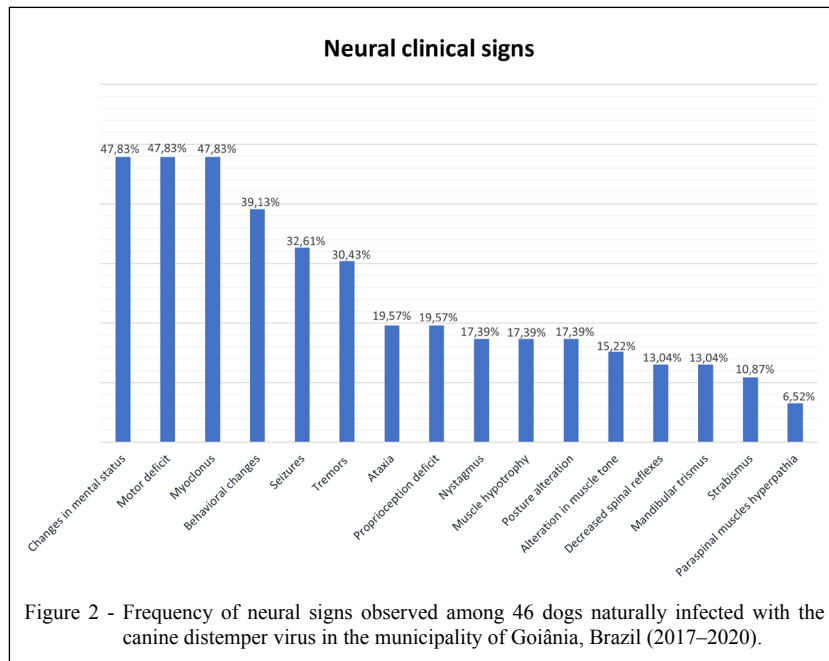
Previous studies demonstrated that all dogs, male and female, PB and UB, and of all ages can be infected with CDV (COSTA et al., 2019; DORJI et al., 2020). However, this study found that puppies (5–11 months) and adults (1–6 years) accounted for approximately 72% of all cases. Similar data have been reported in other studies (HEADLEY & GRAÇA, 2000; SILVA et al., 2007; MARTINS et al., 2020), in contrast to the higher incidence observed among puppies aged up to five months (SILVA et al., 2009).

In other epidemiological surveys, dogs of UBs were shown to have the highest CDV-infection frequencies (HEADLEY & GRAÇA, 2000; COSTA et al., 2019). This may be due to UBs receiving less care than PBs. Many of these dogs are unvaccinated and roam freely in urban and rural areas, coming in direct contact with other dogs and wild animals that are prone to being viral reservoirs. As a result, they get infected, develop the disease, and transmit the virus to other domestic and wild animals (HEADLEY et al., 2012; HEADLEY et al., 2015).

When analyzing infections according to vaccination status, 10.87% (5/46) of infected dogs

Figure 1 - Frequency of extraneural signs observed among 46 dogs naturally infected with the canine distemper virus in the municipality of Goiânia, Brazil (2017–2020).

Neural clinical signs

Figure 2 - Frequency of neural signs observed among 46 dogs naturally infected with the canine distemper virus in the municipality of Goiânia, Brazil (2017–2020).

were completely vaccinated, similar to findings by BUDASZEWSKI et al. (2014), in which 12.20% of infected dogs were vaccinated. Vaccination is regarded as the main preventive measure for CDV infection and should be administered at around 45 days of life, when maternal antibody titers begin to decrease and the puppy becomes more susceptible to different diseases (HEADLEY & GRAÇA, 2000; GREENE & VANDEVELDE, 2012). However, even dogs with a complete vaccination status were infected and developed the disease. These findings highlighted the importance of vaccination as a preventive measure and emphasize that vaccination must be conducted correctly as many factors related to dogs, vaccines, and viral strains could directly interfere with immunization.

The most frequently observed ES were hyporexia or anorexia, nasal or ocular secretions, and dehydration. However, these signs are nonspecific and are also observed among dogs with other isolated or concomitant diseases (HEADLEY et al., 2015; MARTINS et al., 2020). Hyperkeratosis of the foot pads and nose, the most frequent ES associated with CDV, was observed in approximately 30% of dogs. During the acute clinical stage, these signs may result from the localization of CDV in the stratum spinosum and granulosa of the cushions, possibly due to viral dissemination via hematogenous routes and persistence in these tissues. ES can be observed from 1–60 days post-infection (GREENE & VANDEVELDE, 2012).

Multifocal or diffuse, acute or chronic, and progressive signs are generally observed (AMUDE et al., 2007; GREENE & VANDEVELDE, 2012) CDV appears to have tropism in the cerebellar, forebrain, and brainstem cells (SILVA et al., 2009). In this study, the predominant NS indicated involvement of the forebrain and brainstem. However, cerebellar signs, such as dysmetria, hypermetria, cerebellar ataxia, and intention tremor, were not observed in any of the infected dogs. According to KOUTINAS et al. (2002), cerebellar signs can be subclinical, and their absence does not rule out lesions in this structure.

Similar to other studies (KOUTINAS et al., 2002; SILVA et al., 2009; HEADLEY et al., 2012; HEADLEY et al., 2015; MARTINS et al., 2020), we reported motor deficits and myoclonus as the most frequent clinical manifestations. Motor deficits are non-specific signs that involve different neuroanatomical components. Furthermore, myoclonus can result from the destruction of areas in the basal nuclei (prosencephalic areas) or abnormalities in the interneurons of the nuclei of lower motor neurons, involving spinal intumescence (DE LAHUNTA et al., 2014). Some authors consider myoclonus to be the pathognomonic of CDV, whereas others suggested that other illnesses are known to manifest with these signs (i.e., myoclonic epileptic seizures of diverse etiology) (CERDA-GONZALEZ et al., 2021). Although, myoclonia is one of the most common clinical manifestations, 50% of the infected dogs did not present with this clinical sign.

Although, this study did not analyze the risk factors for CDV infection, high lethality was observed among CDV-infected dogs. Additionally, a higher frequency of cases was observed in adults and UB dogs. CDV infection was observed in both vaccinated and unvaccinated dogs. Thus, these results confirmed the importance of including CDV in the differential diagnosis of dogs with ES and NS to establish appropriate treatment and prophylaxis procedures. These results also highlighted that CDV can occur among dogs of different age groups, sex, breeds, and even those with complete vaccination status.

The main limitation of the study was the low sample size, which prevented a statistical evaluation and, thus, the possible identification of risk factors associated with the epizootiology of canine distemper. This also made it impossible to correlate a particular clinical sign with deterioration of the condition towards death. The lack of a control group did not allow a better estimate of the frequency of canine distemper positive animals in a population.

Even so, it is important to emphasize that CDV was identified in a population of dogs of different ages, mainly among adult individuals. Although, most animals were vaccinated, the study showed the development of the disease, despite vaccination, in 10.87% of the animals. For a long time, it was believed that the disease only affected puppies; however, this study corroborates other recent studies that also showed a higher age range of involvement. Extraneural and neural clinical signs were observed, and dogs with neural signs showed higher lethality, indicating the progression of the disease because of viral dissemination.

These data highlight the importance of performing a differential diagnosis of canine distemper even in vaccinated and adult animals, and animals showing extraneural and neural clinical signs. Although, there are no specific drugs for treating canine distemper, early diagnosis and initiation of supportive treatment could reduce lethality rate by restricting the spread of the virus among other animals. The study, even if carried out in a specific region of Brazil, can be useful in understanding CDV infection in other regions as well.

The data presented provided relevant information on the characteristics of CDV-infected dogs in Brazil and highlight the need for broader epizootiological studies to establish predisposing factors related to and prevalence of CDV, and the need to consider differential diagnosis of canine distemper.

CONCLUSION

The presented epizootiological data suggested that dogs of any sex, breed, age, and vaccination status can be naturally infected with CDV; however, most cases occur among UBs, adults, and dogs with an incomplete vaccination status. Most dogs infected with CDV die or undergo euthanasia, particularly when neurological or systemic signs are present. The present data also emphasized that dogs with a complete vaccination status are not completely immune. Understanding the epizootiological characteristics of canine distemper in endemic areas is important as it may facilitate early diagnosis and allow for appropriate prophylactic and therapeutic measures.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest for this article. The founding sponsors had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, and in the decision to publish the results.

AUTHORS' CONTRIBUTIONS

All authors conceived and designed the experiments. KMFM and GDSF performed the biological material collections, clinical assessments, and laboratory analyses. BBJT and MBLDS supervised and coordinated the experiments. KMFM performed statistical analyses of experimental data. KMFM and BBJT prepared the draft manuscript. All authors critically reviewed the manuscript and approved the final version.

BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

This study was approved by the Ethics Committee on Animal Use (CEUA) - Protocols nº 065/16 e nº 106/18 of the Universidade Federal de Goiás (UFG).

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