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Clinical syndromes of nervous distemper in dogs initially presented without conventional evidences of CDV infection

Síndromes clínicas da apresentação neurológica da cinomose em cães admitidos inicialmente sem as evidencias convencionais da infecção pelo CDV[1]

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Abstract

Despite large vaccination practice, canine distemper virus (CDV) is yet an important infectious agent that leads to nervous disease in canine populations worldwide. Unfortunately, the clinical diagnosis of distemper encephalomyelitis is often difficult in cases presented without conventional evidences of CDV infection such as systemic signs and myoclonus. Therefore, the aim of this study was to evaluate the neurological deficits and the clinical syndromes of nervous distemper in dogs suffering from neurological disease admitted in the absence of the conventional evidences of CDV infection. Dogs presented with central nervous disease in which toxic/traumatic or a CDV-free etiology could be excluded *ante mortem* were prospectively followed up and which that died (natural death or euthanasia, despite medical treatment) and necropsy was carried out were included in this study. Ten out of 35 evaluated dogs were *post mortem* diagnosed with CDV encephalomyelitis by both CDV RNA detection through RT-PCR assay in nervous tissue and observation of distemper-compatible neuroparenchymal lesions. According to the nervous signs, clinical history, and the age of presentation, the distemper dogs were grouped in three clinical syndromes of CDV encephalomyelitis: i) canine distemper encephalitis in immature dogs (CDEID) (*n*=3); ii) multifocal distemper encephalomyelitis in mature dogs (MDEMD) (*n*=6); and iii) old dog encephalitis (ODE)-like syndrome (*n*=1). The respective nervous deficits expected from each one of the syndromes herein presented were discussed.
Key words: Dog, canine distemper virus, distemper, encephalomyelitis, RT-PCR

Resumo

Apesar da prática de vacinação, o vírus da cinomose canina (CDV) ainda é um importante agente infeccioso que leva à doença neurológica na população canina em todo o mundo. Infelizmente, o diagnóstico clínico da encefalomielite pela cinomose é difícil nos casos apresentados sem evidências clínicas convencionais de infecção pelo CDV, tais como sinais sistêmicos e mioclonia. Portanto, o objetivo deste estudo foi avaliar os déficits neurológicos e as síndromes clínicas da apresentação neurológica da cinomose em cães portadores de doença neurológica apresentados na ausência de evidências convencionais de infecção pelo CDV. Foram prospectivamente acompanhados cães que apresentaram doença do sistema nervoso central, onde a abordagem diagnóstica *ante mortem* excluiu outras afecções que não cinomose (etiologia tóxica, traumática, degenerativa, neoplásica, etc), sendo

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incluídos neste estudo os animais que vieram a óbito (morte natural ou eutanásia, apesar do tratamento médico) e foram necropsiados. Dez de 35 cães avaliados foram diagnosticados no *post-mortem* com encefalomielite pelo CDV pela detecção de RNA viral pelo RT-PCR no tecido nervoso e observação de lesões neuroparenquimatosas compatíveis com cinomose. De acordo com os sinais neurológicos, a história clínica e a idade de apresentação, os cães foram agrupados em três síndromes clínicas da forma neurológica da cinomose: i) encefalite pela cinomose canina em cães imaturos (CDEID) (n = 3); ii) encefalomielite multifocal pela cinomose em cães adultos (MDEMD) (n = 6); e iii) síndrome similar a encefalite do cão velho (ODE-like) (n = 1). Os respectivos déficits neurológicos esperados para cada uma das síndromes aqui apresentadas foram discutidos.
Palavras-chave: Cães, vírus da cinomose canina, cinomose, encefalomielite, RT-PCR

Introduction

In the practicing of veterinary neurology is notable that different causes such as degenerative, metabolic, autoimmune, nutritional, infectious/inflammatory, toxic, and vascular conditions may lead to neurological disturbs that affect the brain and produce encephalopathy in dogs (BRAUND, 1994; PLATT; OLBY, 2004; DEWEY, 2008). Nevertheless, among all the possibilities, infectious/inflammatory brain conditions are especially important and have been playing an important role in the incidence of encephalopathy in dogs (TIPOLD, 1995; THOMAS, 1998; PLATT, 2006; SCHWAB et al., 2007; AMUDE; ALFIERI, ALFIERI; 2007a).

Canine distemper virus (CDV) is securely an important pathogen of meningoencephalomyelitis in dogs (THOMAS, 1998; GREENE; APPEL, 2006). Besides the extensive practice of vaccination worldwide, CDV is an important re-emerging agent of nervous disease in dogs (JÓŽWIK; FRYMUS, 2002; KOUTINAS et al., 2002; GRIOT et al., 2003; NORRIS et al., 2006), and has also been recorded in epidemic focus even in vaccinated dogs (KELLY et al., 2005; LAN et al., 2006).

Distinct clinical syndromes of CDV encephalomyelitis have been recognized in dogs concerning the neurological presentation, the occurrence of concomitant systemic illness, the age of the dog, the vaccinal and immune status, the recent history of vaccination, the neurological deficits, and the relapsing course of the nervous signs. Such nervous syndromes of distemper are described as: canine distemper encephalomyelitis in immature dogs (CDEID), multifocal distemper encephalomyelitis in mature dogs (MDEMD), chronic relapsing distemper encephalomyelitis (CRDE), post-vaccinal distemper encephalitis (PVE), and old dog encephalitis (ODE) (HARTLEY, 1974; CORNWELL et al., 1988; HIGGINS; CHILD; VANDEVELDE, 1989; SHELL, 1990; BRAUND, 1994; SUMMERS; CUMMINGS; DELAHUNTA, 1995; VITE, 2005; HEADLEY et al., 2009).

While the literature about CDV neuropathology is relatively wide (SUMMERS; APPEL, 1994; HEADLEY; SOARES; GRAÇA, 2001; AMUDE; ALFIERI; ALFIERI, 2007a; SILVA et al., 2007; SILVA et al., 2009), clinical studies focused purely on nervous signs of distemper in dogs presented exclusively with the neurological disease in absence of conventional CDV infections findings (systemic signs and myoclonus) are not often (TIPOLD; VANDEVELDE; JAGGY, 1992; VANDEVELDE; CACHIN, 1993; AMUDE et al., 2006d). Clinical syndromes of CDV infection has been cited in classical textbook (BRAUND, 1994; SUMMERS; CUMMINGS; DELAHUNTA, 1995; VITE, 2005) and review articles (SHELL, 1990; AMUDE; ALFIERI; ALFIERI, 2006b), however, there are only one multiple dog study (VANDEVELDE et al., 1980) that categorize nervous distemper in clinical syndromes of CDV infection. Thus, the approach by clinical syndromes of CDV encephalomyelitis has not been currently performed, although neuro-clinical aspects of distemper have been evaluated (THOMAS; SORJONEN; STEISS, 1993; TIPOLD et al., 1994; TIPOLD, 1995; SILVA et al., 2007).

Accordingly, the aim of this study was to evaluate the clinical syndromes and the respective

neurological deficits of nervous distemper from dogs presented with central nervous disease in the absence of the systemic signs and myoclonus. The dogs were followed up from hospital admission until clinical resolution (recovering, euthanasia, or natural dead), and only were accessed for this study dogs in which the definitive *post mortem* diagnosis were carried out. The nervous signs and clinical presentation expected for each one of the clinical syndromes were discussed.

Materials and Methods

Animals, and inclusion and diagnostic criteria

From 2003 to 2005 we prospectively evaluated dogs presented to the Veterinary Teaching Hospital with central nervous disease in the absence of systemic signs (respiratory and/or gastrointestinal involvement) and myoclonus at the time of hospital admission. Dogs that eventually displayed systemic signs or myoclonus after the initial hospital presentation were not excluded from the study. Dogs in which toxic/traumatic or CDV-free etiology could be diagnoses *ante mortem* by the medical routine procedures were excluded.

The dogs presented with nervous disease were followed up and only the animal which died (natural death or euthanasia, despite medical treatment) and necropsy was carried out were included in this study. The animals were daily monitored and all the data about the neurological examination and clinical evolution was recorded. At *post mortem* central nervous system (CNS) fragments were submitted for CDV detection by reverse transcription-polymerase chain reaction (RT-PCR) and histological evaluation (light microscopy) by routine procedures (H&E).

The animals were admitted at the Veterinary Teaching Hospital and the owner's consent was obtained before the clinical evaluation and samples collection. The approach by clinical syndromes of CDV encephalomyelitis was carried out regarding previously established criteria (HARTLEY, 1974; VANDEVELDE et al., 1980; CORNWELL et al., 1988; HIGGINS; CHILD; VANDEVELDE, 1989; SHELL, 1990; BRAUND, 1994; VITE, 2005).

RT-PCR

For CDV detection by RT-PCR assay, the RNA was extracted from an aliquot of 300 µL of suspension (10% w/v) of fresh CNS fragments in phosphate-buffered saline (PBS) pH 7.2, according to the silica/guanidine isothiocyanate method (BOOM et al., 1990). Aliquots of ultrapure (MilliQ®) sterile water were included as negative control in all the RNA extraction procedures.

The RT-PCR assay was performed using the oligonucleotides primers CDV 1 (sense) [5'-aca gga ttg ctg agg acc tat-3', nt 769-789] and CDV2 (anti-sense) [5'-caa gat aac cat gta cgg tgc-3', nt.1055-1035]. The sequences of the primers were designed to amplify an amplicon of 287 bp length of the CDV nucleoprotein (NP) gene (FRISK et al., 1999). The RT-PCR was carried out as previously described (AMUDE; ALFIERI; ALFIERI, 2006a). All reactions were performed using clinical samples from a dog with fungal meningoencephalitis (*Cryptococcus neoformans*) as a negative control. CDV Rockborn strain infected MDCK (Madin Darby canine kidney) cells were used as CDV positive control.

The amplified products were analyzed by electrophoresis in 2% agarose gel with ethidium bromide (0.5 µg/mL) in TBE buffer pH 8.4 (89 mM Tris-HCl; 89 mM boric acid; 2 mM EDTA) in constant voltage (90 V) for approximately 45 minutes and visualized under UV light. The identities of the RT-PCR amplicons were confirmed by restriction fragment length polymorphism (RFLP) with *Hinf* I enzyme (Invitrogen™Life Technology, USA) digestion.

Histology

CNS sections were examined for CDV-induced lesions. For this, brain and spinal cord samples were fixed in 10% buffered neutral formalin,

embedded in histological paraffin, sectioned at 5 µm and stained with hematoxylin and eosin (H&E) following routine procedures. The histopathological diagnosis of nervous distemper followed parameters previously described (SUMMERS; CUMMINGS; DELAHUNTA, 1995; HEADLEY; SOARES; GRAÇA, 2001; KOUTINAS et al., 2002; GEBARA et al., 2004a; AMUDE; ALFIERI; ALFIERI, 2007a; SILVA et al., 2007; SILVA et al., 2009). Briefly, intranuclear and cytoplasmic eosinophilic inclusion body in the nervous cells (mainly astrocytes), focal to multifocal vacuoles in the white matter (spongy change suggestive of distemper demyelination), and influx of mononuclear inflammatory cells in perivascular sites (perivascular cuffing) and into neuroparenchyma, were considerate as suggestive of CDV encephalitis.

Results

Thirty five dogs fulfilled the inclusion and diagnostic criteria and were evaluated in this study. In the CNS of 10 dogs, the RT-PCR assay amplified products of 287 bp size that was cleaved by *Hinf* I as expected to the CDV, and yielded fragments of 227 and 60 bp size. The histopathological findings consistent with CDV induced neuroparenchymal changes were observed in the CNS of these 10 cases in which CDV was detected by RT-PCR; however, not all the CDV induced nervous lesion (inclusion body, vacuolar change, and neuroparenchymal inflammation) occurred in the same nervous section evaluated. None of the dogs (*n*=25) in which CDV was not detected in the CNS by RT-PCR assay showed neuroparenchymal lesions compatible with CDV infection, and the data (neuroclinical and neuropathological aspects) of the non-distemper dogs will not be presented and discussed in this study.

The data (age, breed, sex, and vaccination records) of the distemper dogs are presented in the Table 1. The onset of neurological signs was acute in tree dogs (nº 06, 07, and 09) and gradual with a progressive course in the remaining 7 distemper dogs. One dog (nº 03) displayed myoclonus 22 days after the beginning of neurological presentation, and two dogs demonstrated systemic signs after admission, one (nº 07) on the 4th day (vomiting and diarrhea), and the other (nº 08) on the 18th day (diarrhea) of clinical evolution. According to the age, neurological signs, clinical findings and history, the distemper dogs were grouped as following: CDEID (nº 04, 09, and 10), MDEMD (nº 01, 03, 05, 06, 07, and 08), and ODE-like disease (nº 02). The clinical syndromes of nervous distemper and the respective neurological deficits of the dogs with CDV encephalomyelitis are presented in Table 2.

Table 1. Distribution of the data (dog identification, age, breed, sex, and vaccination records) of the distemper dogs (*n* = 10).

Dog	Age (month)	Breed	Sex	Vaccination records *
01	36	Mixed breed	F	Unvaccinated
02	132	Mixed breed	F	Unvaccinated
03	62	Collie	F	Vaccinated
04	7	Mixed breed	M	Vaccinated
05	18	German shepherd	M	NA
06	21	Cocker spaniel	M	NA
07	145	Cocker spaniel	F	Vaccinated
08	55	Boxer	M	Vaccinated
09	3	Cocker spaniel	F	Vaccinated
10	12	Mixed breed	F	Unvaccinated

***** It was considered vaccinated dogs that had one or more vaccination record. Dogs 03, 07, and 08 were in day with the vaccination schedule (annual buster); dog 09, 10, and 04 were undergoing a vaccination schedule, but had yet received only one (09 and 10) and two (04) vaccination.
Source: Elaboration of the authors.

Table 2. Clinical syndromes, dog identification, respective neurological deficits, and age of presentation from the dogs with distemper encephalomyelitis (n = 10).

Syndrome[a]	Dog	Neurological deficits recorded during medical follow up and age of presentation.
CDEID	04	Compulsive walking, focal seizure with secondary generalization, inappropriate consciousness contend (dullness), positional vertical nystagmus, menace deficit, spastic tetraparesis, postural reactions deficits, decerebellate rigidity[b]. 7-month-old.
MDEMD	09	Generalized seizures not responsive to medical treatment, coma, spastic tetraparesis, absence of postural reactions, horizontal spontaneous nystagmus. 3-month-old
	10	Ataxia, spastic tetraparesis, postural reactions deficits, blindness, behavioral changes (aggressiveness), stupor. 12-month-old
	01	Weakness of hind limbs, spastic tetraparesis/plegia, absence of postural reactions, truncal and head ataxia, rotatory spontaneous bilateral nystagmus, vestibular strabismus[c]. 36-month-old.
	03	Weakness of the hind limbs, truncal and head ataxia, vertical positional nystagmus, postural reactions deficits, spastic tetraparesis/plegia, myoclonus in the left hind limb and mastigatory muscle. 62-month-old.
	05	Weakness of the hind limbs, truncal and head ataxia, spastic tetraparesis/plegia, postural reactions deficits, pain to spinal cord palpation. 18-month-old.
	06	Truncal and head ataxia, spastic tetraparesis, positional vertical nystagmus with change to rotatory when the head changed positions, severe hypermetria, postural reactions deficits, decerebellate rigidity. 21-month-old.
	07	Spastic paraplegia following to flaccid paraplegia, absence of postural reactions in the hind limbs. 145-month-old.
	08	Ataxia, head tilt to the right, spastic tetraparesis/plegia, positional horizontal nystagmus, postural reactions deficits. 55-month-old.
ODE-like	02	Seizure-like activity reported by the owner, behavioral change (aggressiveness), alert but with an inappropriate consciousness contend, compulsive walking, circling (open circle) to the right and to the left, mild ataxia, head pressing, postural reactions deficits, mild hypermetria (hyperkinesia), tetraparesis. 132-month-old.

[a] CDEID (canine distemper encephalomyelitis in immature dogs); MDEMD (multifocal distemper encephalomyelitis in mature dogs); ODE (old dog encephalitis);
[b] Opisthotonos with spasticity and rigidity of thoracic limb.
[c] Positional ventrolateral strabismus when the head was dorsally extended.
Source: Elaboration of the authors.

Discussion

The RT-PCR and RFLP results, associated with the histopathological findings consistent with distemper encephalomyelitis, suggest that CDV was the etiological agent of the neurological disease in 10 out of 35 dogs included in this clinical study. The importance of the cases herein presented lies on the diagnosis of CDV encephalomyelitis in instances initially admitted with central nervous disease in the absence of conventional signs of distemper such as systemic signs and myoclonus (at least at the first days of admission). In order to contribute with both veterinarian clinicians and veterinary scientific literature, we established inclusion criteria that selected mainly animals presented without the classical clinical picture of distemper. The most of the current papers about nervous distemper (clinical, pathological, molecular, and diagnostic aspects) have been working with dogs presented with typical signs of CDV infection such as myoclonus and respiratory/gastrointestinal signs (SHIN et al., 1995; MORITZ; FRISK; BAUMGÄRTNER, 2000; JÓŽWIK; FRYMUS, 2002; KOUTINAS et al., 2002; GEBARA et al., 2004b; SAITO et al., 2006; LAN et al., 2006; SILVA et al., 2007); however, the clinical diagnosis of distemper encephalomyelitis

is often difficult in cases presented without these conventional evidences of CDV infection (TIPOLD; VANDEVELDE; JAGGY, 1992), and in such situations the clinical diagnosis of nervous distemper may be a challenge for the clinicians (TIPOLD; VANDEVELDE; JAGGY, 1992; VANDEVELDE; CACHIN, 1993; MORITZ; FRISK; BAUMGÄRTNER, 2000; AMUDE et al., 2006c; AMUDE et al., 2007b). Additionally, although distemper in immature dogs has been the most common presentation of CDV infection (BRAUND, 1994; FRISK et al., 1999; KOUTINAS et al., 2002; VITE, 2005), in this investigation distemper encephalomyelitis in mature dogs were presented. In South America, especially in Brazil, distemper is an endemic viral infectious disease (HEADLEY; GRAÇA, 2000; AMUDE et al., 2006d; SILVA et al., 2007), and the knowledge about non-conventional nervous distemper in mature dogs might help clinicians that have been working in the field of veterinary neurology.

Partial seizures characterized as "chewing-gum fits" (twitching of facial/masticatory muscles) with secondary generalization (tonic-clonic movements in all skeletal muscles), vertical positional nystagmus (deficit of the 8th cranial nerve), and spastic tetraparesis were nervous deficits observed in one 7-month-old dog (nº04) presented with CDEID. The other 2 dogs (nº 09 and 10) suffering from CDEID had also multifocal nervous disease characterized by cerebral dysfunction (generalized seizures and behavioral changes, respectively), vestibular deficits (nystagmus), impaired level of consciousness, blindness, and non-ambulatorial spastic tetraparesis. While seizure is a cortical/thalamic dysfunction, nystagmus associated with spastic tetraparesis suggests a central vestibular disturb due to brainstem involvement (BRAUND, 1994; DE LAHUNTA; GLASS, 2009). The impairment of consciousness level also suggests dysfunctions of the **ascending reticular** activating **system** (ARAS) that lies on the brainstem (DE LAHUNTA; GLASS, 2009; DEWEY, 2008). Although the clinical signs of seizures depend on which part of the cerebrum is affected, many seizures observed in distemper dogs are described as "chewing-gum fits" (SHELL, 1990; AMUDE et al., 2006c).

Neurological signs of CDEID are quite varied and usually suggest a multifocal involvement of the CNS (SHELL, 1990; VITE, 2005). Signs of localization in cortical and subcortical areas (seizures, behavioral changes), brainstem (cranial nerves deficits and impaired level of consciousness) and cerebellum (hypermetria) may be often observed, while spinal cord (paresis/paraplegia) signs are infrequent (BRAUND, 1994). CDEID is the most common form of CDV infection, but in our study this clinical syndrome was not the most common due to a bias of selection designed for this study. CDEID is often characterized by systemic evidence of gastrointestinal and respiratory disturbances (BRAUND, 1994; VITE, 2005), and these signs were exclusion criteria for our study.

In the CDEID cases presented herein no previous gastrointestinal disturbance was reported by the owner probably because two animals was yet undergoing the vaccination schedule, while the other had received two doses of life attenuated vaccine. Intermediate titers of anti-CDV antibodies may protect animals from systemic disease, but are not enough to block the nervous tissue infection (GREENE; APPEL, 2006). Coughing was related almost one month before the neurological presentation of one dog (nº 04); nevertheless, as no diagnostic procedure was performed at that time, it is difficult to affirm that CDV was the coughing causative, however this possibility also cannot be ruled out. Myoclonus, a rhythmic jerking of single muscles or muscle groups, is a characteristic sign of distemper encephalomyelitis in immature dogs (BRAUND, 1994; VITE, 2005; KOUTINAS el al., 2002), however it was lacking in our CDEID cases. Although myoclonus is highly suggestive of CDV infection it may be lacking in 1/3 of the dogs with nervous distemper (TIPOLD; VANDEVELDE;

JAGGY, 1992). In addition, this sign may be also observed episodically with other inflammatory diseases of the CNS (TIPOLD; VANDEVELDE; JAGGY, 1992; GREENE; APPEL, 2006; AMUDE; ALFIERI; ALFIERI, 2007a).

The initial neurological presentation of MDEMD may consist of signs of weakness on the hind limbs, generalized incoordenation (ataxia), and occasional falling. Often these signs progress to spastic tetraparesis/plegia (VANDEVELDE et al., 1980; SHELL, 1990; BRAUND, 1994). In 4 (nº 01, 03, 05, and 08) out of 6 cases of MDEMD herein presented these initial neurological presentation was recorded, and in 5 cases (nº 01, 03, 05, 06, and 08) the neurological condition progressed to tetraparesis/plegia in a recumbent form. At the moment of hospital admission or during the clinical monitoring, signs of localization in cerebellum (intentional tremor, head and trunk ataxia, and dysmetria with hypermetria), brainstem (vertical positional nystagmus, rotatory spontaneous nystagmus, positional ventrolateral strabismus, and head tilt), and spinal cord (paraplegia) were easily recognized single or in various combinations in the dogs with MDEMD. All the signs of localization in the brainstem reflected central vestibular disease manifested as deficits of the 8th cranial nerve. Myoclonic movements are usually not observed with MDEMD, although head tremors may be seen (VANDEVELDE et al., 1980; VITE, 2005). Nevertheless, in one case (nº 03) myoclonus was observed during clinical evolution on 22th day after the beginning of the neurological deficits. In agreement to the literature (VANDEVELDE et al., 1980; SHELL, 1990; BRAUND, 1994; VITE, 2005), cortical and subcortical signs (seizures, compulsive walking, and behavioral changes) were not features of this syndrome and affected animals maintained a normal mental status during the clinical following up.

MDEMD is a type of multifocal encephalomyelitis in mature dogs with relatively low incidence that is characterized by a chronic course and does not appear to be related to breed or sex (VANDEVELDE et al., 1980; VITE 2005; AMUDE et al., 2007b). Vaccinated animals may also be affected, as observed in 3 out of 6 MDEMD dogs. During the course of the MDEMD, signs of localization in cerebellum, brainstem, and spinal cord are common (VANDEVELDE et al., 1980; SHELL, 1990; BRAUND, 1994), and were recognized single or in associations in 5, 5, and 1 instance, respectively, during following up.

Although MDEMD is typically a multifocal CDV encephalomyelitis (VANDEVELDE et al., 1980; VITE, 2005; AMUDE et al., 2007b), two dogs suffering from this syndrome demonstrated signs suggestive of focal CNS lesion at the first neurological examination. One dog (nº 07) was presented with focal spinal cord signs (spastic paraplegia), and the other (nº 06) with typical focal cerebellar involvement (truncal and head ataxia, intentional tremor of the head, and dysmetria with severe hypermetria). In the first case (nº 07) the myelography was performed (data not show) and no compressive lesion was recognized. This dog remained hospitalized and during clinical monitoring was possible to recognize a progressive multifocal spinal cord disease. Such cases, which are initially presented with focal spinal cords signs and in which other typical findings of CDV infection (extraneural signs or myoclonus) are absent at the time of presentation, are a diagnostic challenge for the veterinarian surgeon (TIPOLD; VANDEVELDE; JAGGY, 1992; VANDEVELDE; CACHIN, 1993). In the other case (nº 06), with the evolution of the disease, it was also recognized a progressive multifocal (cerebellum and brainstem) neurological disease. These observations suggest that the result of only one neurological exam is not enough to state the nervous condition, and the clinical monitoring with successive examinations of the nervous system is essential for prognostic evaluation, and to evaluate the integrity of the nervous pathways during the progression of the disease.

The literature claims that MDEMD is not preceded by, nor is it coincident with the systemic signs, as often seen in young dogs (VANDEVELDE et al., 1980; BRAUND, 1994; VITE, 2005; AMUDE et al., 2007b). However, in this study two dogs with MDEMD demonstrated gastrointestinal signs after the manifestation of neurological deficits; but the etiology remained unclear since no diagnostic procedure was performed to rule out nor confirm other causes of such manifestations. Many causes other than CDV infection could be contributing to theses systemic signs, including medical treatment, hipoperfusion of the gastrointestinal tract due to hiporexia/ anorexia, hepatopathy, nephropathy, and others.

Neurological findings showed by one 11-year-old distemper dog (nº 02) such as behavioral change (aggressiveness), inappropriate consciousness content, head pressing against objects, circling and compulsive walking, are cortical and subcortical signs compatible with ODE-like syndrome. ODE is a rare subacute to chronic progressive panencephalitis with very low incidence around the world that is believed to be caused by CDV infection (CORDY, 1942; SHELL, 1990; BRAUND, 1994; VITE, 2005), since CDV antigens, nucleocapsids, and CDV nucleoprotein RNA were already demonstrated in the brain of dogs with ODE (LINCOLN et al., 1971; LILCON et al., 1973; HEADLEY et al., 2009). Affected dogs are usually older than six years of age, but younger dogs (3 years) were also described with ODE-like syndrome (LINCOLN et al., 1971). Usually there are no related systemic signs, and the only clinical signs are related to the cortical and subcortical involvement (CORDY, 1942; VANDEVELDE et al., 1980; HEADLEY et al., 2009).

In contrast to the signs associated with nervous distemper in immature dogs, signs of brainstem (cranial nervous deficits), and spinal cord disease (paraplegia) are usually absent in cases of ODE (LINCOLN et al., 1971; BRAUND, 1994), as observed in this ODE-like case; in addition, there is also a relative sparing of cerebellar signs (VANDEVELDE et al., 1980). Nevertheless, in this ODE-like case some "cerebellar" signs were observed (even without aparent HE lesions on cerebellum sections – data not shown), such as hyperkinesia (exaggerated and uncoordinated hind limb placement). Hyperkinesia was also already reported in an experimental ODE case (AXTHELM; KRAKOWKA, 1998). Seizure is an unusual finding of ODE (CORDY, 1942; LINCOLN et al., 1971; LILCON et al., 1973; VANDEVELDE et al., 1980; SHELL, 1990; BRAUND, 1994; VITE, 2005). During the clinical following up, no seizure was observed in this ODE-like case, however seizure-like activity was reported by the owner at the time of first examination. Episodic seizure may likely reflect localization of the virus in the cerebral cortical neurons, and was already previously reported in an experimental (AXTHELM; KRAKOWKA, 1998), and in a naturally occurring ODE case (HEADLEY et al., 2009).

Conclusion

Extra-neural signs and myoclonus may be common and characteristic of the CDV infection. Nevertheless, central nervous disease in the absence of these signs may potentially be a clinical syndrome of distemper, such as ODE or MDEMD. Unfortunately, the clinical diagnosis of CDV infection may be only carried out in "conventional" cases. The conventional presentation of nervous distemper is characterized by immature dogs with myoclonus and others nervous deficits preceded by or concomitant with the systemic illness. However, even these conventional signs of distemper may also be absent in some immature dogs (BRAUND, 1994), such as verified in the cases of CDEID herein presented. Since distemper is an infectious disease with poor prognosis in which there is no effective antiviral treatment, early diagnosis of distemper is important. Information concerning the neuro-clinical aspects and respective clinical syndromes of

distemper encephalomyelopathy herein presented may allow the clinicians to include nervous distemper as differential diagnosis in the list of nervous disease of dogs, especially in instances in which the conventional signs of CDV infection may be absent at the moment of first examination.

According to the literature MDEMD is a rare distemper clinical syndrome (BRAUND, 1994; VITE, 2005; AMUDE et al., 2007b), but it may be recognized more often than previously stated, especially in areas where CDV infection is endemic such as Brazil. However, ODE is an extremely rare non-conventional syndrome and may be not confused with conventional distemper in an old dog (VANDEVELDE et al., 1980; SUMMERS; APPEL, 1994). Aged dogs may be affected by conventional nervous distemper and will demonstrate multiple nervous signs other than cortical/subcortical involvement, and in the most of such cases typical CDV induced neuroparenchymal lesions will be recognized in the cerebellum. ODE is so rare that herein we referred to the dog n° 02 as an ODE-like syndrome because the clinicopathological presentation resembled what's is known as ODE; nevertheless, more pathological, virological, and molecular studies haven been carried out to certify if this case may represent a real case of ODE.

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