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NEUROLOGICAL MANIFESTATIONS OF DISTEMPER IN DOGS AND THEIR RELATIONSHIP WITH CEREBROSPINAL FLUID VIRAL LOAD

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ABSTRACT

Objective: To analyze the relationship between the viral load of the canine distemper virus in the cerebrospinal fluid and the severity of neurological manifestations in dogs,

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evaluating the main diagnostic methods, the progression of the disease and possible therapeutic approaches. Canine distemper is a highly contagious viral disease that can cause severe neurological impairment, with demyelinating encephalitis being one of the main consequences of infection in the central nervous system (CNS). The breakdown of the blood-brain barrier, driven by matrix metalloproteinases and an intense inflammatory response, allows the virus to enter the cerebrospinal fluid, increasing the severity of symptoms. Studies show that dogs with a high concentration of virus in the cerebrospinal fluid exhibit more severe clinical conditions, such as myoclonus, ataxia, seizures and proprioceptive deficits, in addition to a higher mortality rate. The diagnosis of neurological distemper can be complex due to its similarity to other neurological diseases. CSF RT-PCR is one of the most sensitive and specific techniques to confirm infection. With regard to treatment, there is still no efficient specific antiviral, but studies indicate that ribavirin can decrease the replication of the virus and increase the survival of infected dogs. Understanding the connection between viral load and neurological manifestations is crucial to improve diagnostic, prognostic and treatment tactics, aiding in the clinical control of canine distemper.

Keywords: Canine Distemper. Demyelinating encephalitis. CSF. Viral Neuroinfection. RT-PCR.

INTRODUCTION

Canine distemper is a highly contagious infectious disease caused by *the Canine Distemper Virus* (CDV), belonging to the *Paramyxoviridae* family, genus *Morbillivirus*. This disease mainly affects young unvaccinated dogs and can affect various body systems, such as the respiratory, gastrointestinal and, above all, the CNS (Vandevelde and Zurbriggen, 2005; Greene and Appel, 2006).

It is one of the most lethal viral diseases reported in dogs in Brazil. Although it was first described in dogs in 1761 in Spain, research on the virus today does not show satisfactory progress, perhaps this being the main reason why there are still no treatments with truly effective results. (Appel *et. al*., 1972; Chagas, *et.al*., 2023).

Studies show a wide genetic variety, with more than 11 genetic lineages already detected, 4 of them in South America. In addition, more in-depth studies on the lineages of several countries, it was found that many resemble each other, for example, the Brazilian SA1 lineage is identical to the European EU1, leading to consider the possibility of the existence of the virus since the time of Pangea. (Panzera *et al*., 2014)

The neurological symptoms of distemper are one of the most critical elements of the disease resulting from neurological alterations characterized by demyelinating lesions of the central nervous system (CNS), viral replication within oligodendrocytes and microglial cells, regulation of the class I histocompatibility complex (MHCI) and infiltration of inflammatory cells, these alterations induce neurological clinical signs (Gebara *et al*., 2004; Mangia; Paes, 2008; Schobesberger *et al*., 2002; Vandevelde; Zurbriggen, 2005).and they can appear both in the acute phase and in more advanced phases, after the resolution of systemic symptoms. CNS complications result in symptoms such as myoclonus, ataxia, nystagmus, seizures, and proprioceptive deficits, with demyelinating encephalitis standing out as the main neuropathological manifestation (Amude *et al*., 2007; Beineke *et al*., 2009). Neurological manifestations depend on the region of the CNS affected (Silva, 2009; Martella *et al*, 2008; Amude *et al*., 2006). There are several syndromes described, including encephalitis in elderly dogs and post-vaccination encephalitis with an unfavorable prognosis (Greene; Apple, 2006).

It is believed that there is a higher incidence of the disease in periods when there are failures in the animal's immune system, enabling infection at any age, usually in

animals aged 60 to 90 days that have not had adequate colostrum intake or due to failure in the vaccination protocol (Freire, *et al.,* 2019).

The entry of CDV into the CNS has not yet been fully elucidated, but studies indicate that infection can occur through the cerebrospinal fluid, carried by infected leukocytes, reaching choroid plexus and ependymal cells (Higgins *et al*., 1982; Vandevelde and Zurbriggen, 1995; Carvalho *et al*., 2012). This process results in the activation of microglial cells and the infiltration of CD8+ lymphocytes, contributing to the worsening of demyelinating lesions (Wünschmann *et al*., 1999).

Therefore, the evaluation of the cerebrospinal fluid becomes a crucial instrument for the diagnosis and follow-up of neurological distemper. Some studies indicate that dogs with a high viral load in the cerebrospinal fluid tend to have more severe neurological symptoms, with a higher probability of mortality and lasting consequences (Elia *et al*., 2007). RT-PCR has been a fundamental technique in the detection and quantification of CDV in the CNS, allowing a more accurate assessment of disease progression and aiding in prognosis (Józwik and Frymus, 2005; Shin *et al*., 2004).

In this context, the purpose of this study is to investigate the connection between the neurological manifestations of canine distemper and the amount of virus present in the cerebrospinal fluid, examining the clinical and laboratory results reported in the literature. Understanding this interaction can help in more accurate diagnoses and more accurate treatment strategies for disease control.

METHODOLOGY

This study consists of a narrative analysis of the literature that addresses the connection between the viral load of the canine distemper virus (CDV) in the cerebrospinal fluid and neurological manifestations in dogs. Scientific articles, dissertations and theses available in databases such as PubMed, ScienceDirect, Scielo and Google Scholar were examined. The selection criteria included research published in the last 25 years, which dealt with CDV infection in the central nervous system, laboratory diagnosis, clinical evolution of the disease and therapeutic approaches. Studies that did not have a defined methodology or whose data were not directly relevant to neurological distemper were discarded. The choice of research was made through the examination of titles and abstracts, followed by a detailed analysis of the pertinent texts.

The information obtained included data on diagnostic techniques, viral load in the blood, immune response and clinical progress of the cases examined. RT-PCR was highlighted as one of the most effective methods to identify CDV in the cerebrospinal fluid, when compared to other laboratory techniques, such as immunofluorescence and seroanalysis. Additionally, the therapeutic strategies employed in dogs with neurological symptoms were examined, which include the use of ribavirin and blood-brain barrier modulators. The compilation of the findings enabled a qualitative evaluation of the link between viral load and symptom severity, contributing to the understanding of the pathogenic processes of the disease and to the search for more efficient diagnostic and therapeutic methods.

RESULTS AND DISCUSSIONS

The relationship between the viral load of CDV in the cerebrospinal fluid and the severity of neurological manifestations has been widely investigated, with evidence indicating a significant impact of the virus on the CNS. The studies analyzed indicate that dogs with a high concentration of cerebrospinal fluid virus tend to have more severe neurological conditions, marked by symptoms such as ataxia, myoclonus, seizures, nystagmus, and paresis (Amude *et al.,* 2007; Beineke *et al*., 2009).

CNS CDV infection occurs through the breakdown of the blood-brain barrier (BBB), mediated by matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9. These enzymes cause the degradation of the extracellular matrix, enabling the entry of infected leukocytes and the spread of the virus (Aoki, 2014). This deterioration favors a high inflammatory response, leading to demyelination and the evolution of neurological symptoms (Vandevelde and Zurbrigen, 2005).

Evaluation of the cerebrospinal fluid of dogs infected with CDV reveals an increase in viral load, along with biochemical changes such as lymphocytic pleocytosis and hyperproteinorrhachia, signaling the existence of ongoing inflammation in the CNS (Elia *et al*., 2007). In addition, the identification of viral RNA in the cerebrospinal fluid by RT-PCR has been shown to be a crucial diagnostic resource for confirming CNS infection, surpassing other methods, such as direct immunofluorescence (Józwik and Frymus, 2005; Shin *et al*., 2004).

Research suggests that viral continuity in the central nervous system may be linked to the emergence of chronic forms of the disease, such as encephalitis in the

elderly dog and secondary multifocal encephalitis. In several situations, even after the disappearance of systemic symptoms, the presence of CDV in the cerebrospinal fluid remains visible, indicating that the virus may remain latent or provoke a constant immune response against the nervous tissue (Wünschmann *et al.,* 1999).

The relationship between viral load and neurological symptoms also indicates that varied patterns of immune response can influence the severity of the disease. Dogs with an efficient immune response to CDV exhibit a reduced viral load and less severe neurological symptoms, in contrast to animals with an insufficient or delayed immune response, which tend to have recurrent infections and a more rapid progression of demyelinating encephalitis (Carvalho *et al.,* 2012). Based on this evidence, the monitoring of the viral load in the cerebrospinal fluid is crucial for a more accurate diagnosis of neurological distemper, enabling a more accurate prognostic evaluation and contributing to the development of more efficient therapeutic strategies.

VIRAL CLASSIFICATION

The etiological agent of canine distemper is an enveloped virus, with pleomorphic morphology and predominantly spherical, approximately 150 nm in diameter. It has a genome composed of single-stranded, unsegmented, negative-polarity RNA, with about 15,690 nucleotides. This genome encodes eight viral proteins, which are responsible for replication, structure, and evasion of the host's immune response (Carvalho *et al*., 2012).

INDIVIDUAL VARIABILITY IN DISEASE PROGRESSION

The clinical progression of canine distemper is quite varied, being affected by elements such as age, immune status, host genetics, and even the viral variant involved. Research indicates that young and immunosuppressed dogs tend to develop more serious and long-lasting conditions, while adult or vaccinated animals may exhibit later and less intense neurological signs (Summers *et al*., 1995).

The immune response plays a key role in the progression of the disease. Dogs with an effective cellular immune response are able to stop viral replication more quickly, reducing the amount of virus in the cerebrospinal fluid and attenuating the severity of nervous symptoms. On the other hand, animals with insufficient or delayed immune response demonstrate greater persistence of the virus in the CNS, resulting in

the evolution of demyelinating encephalitis and a worsening of the prognosis (Carvalho *et al*., 2012).

In addition, differences in neurovirulence between different strains of CDV may affect the severity of the clinical picture. Some strains have greater CNS tropism and are more likely to cause persistent infections, while others are mostly respiratory or gastrointestinal (Martella *et al.,* 2008). Such genetic variations may explain regional variations in the clinical manifestation of distemper.

Some strains of CDV are widely used in the main vaccines available on the market. The Onderstepoort strain, for example, is considered safe and effective, as it does not induce disease after vaccination. However, it may present less stimulation to the humoral immune response compared to other strains. The Rockborn strain is known to induce a more robust immune response, resulting in high antibody titers and prolonged protection. However, there are reports of central neurological manifestations in dogs vaccinated with this strain, which limits its use in vaccination programs (Freire *et al*., 2019).

THERAPEUTIC APPROACH AND CONTAINMENT STRATEGIES

There is currently no specific antiviral treatment for neurological distemper, and treatment is based on clinical and symptomatic support. However, experimental research indicates that certain drugs may exert a positive effect on controlling viral replication and modulating the inflammatory response.

Use of Ribavirin

Ribavirin, a similar nucleoside with antiviral activity, has been studied as a therapeutic option for the neurological stage of distemper. Mangia (2008) evidenced that ribavirin at a dose of 30mg/kg for 15 days has an inhibitory action on viral replication "in vitro", thus reducing the viral concentration in the cerebrospinal fluid and increasing the survival of infected dogs, particularly when administered in advance. In experimental treatments, use associated with DMSO indicated increased tissue perfusion and inhibitory effect on the advance of the virus. However, its application is restricted by the possible negative impacts on the bone marrow and digestive system, as well as the requirement for more research to confirm its real efficacy and safety.

Inhibition of metalloproteinases

The involvement of the BBB is one of the main elements that facilitate the penetration of CDV into the nervous system. Research indicates that matrix metalloproteinase inhibitors (MMP-2 and MMP-9) may be an effective tactic to minimize neuronal injury and decrease inflammation in the Central Nervous System (Beineke *et al*., 2009).

Immunomodulatory therapies

The administration of corticosteroids, such as prednisolone, is a frequent strategy in the treatment of neurological distemper, due to their ability to decrease inflammation in the CNS. However, continuous use can impair the host's immune response, facilitating viral multiplication and intensifying the evolution of the disease (Carvalho *et al*., 2012). Therefore, the use of corticosteroids should be carefully evaluated, especially in situations of severe cerebral edema or a marked inflammatory response.

In addition to corticosteroids, other immune modulation strategies are being studied. The use of monoclonal antibodies as a viable alternative to prevent viral replication without impairing the patient's immunity has been investigated. Similarly, immunoglobulins administered intravenously have shown the ability to modulate the immune response and alleviate neurological symptoms, even though their effectiveness has not yet been widely proven in clinical research (Carvalho *et al*., 2012).

Experimental research indicates that inhibitors of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), may help decrease neuronal damage linked to distemper virus infection. However, the clinical application of these immunomodulators is still restricted due to the scarcity of conclusive information about safety and effectiveness in infected dogs (Beineke *et al*., 2009). Thus, the selection of immunomodulatory therapy should consider the phase of infection and the severity of the inflammatory reaction, preventing interventions that may impair the neurological recovery of affected dogs.

Use of mesenchymal trunk cells (MSCs)

Mesenchymal stem cells (MSCs) have generated a great deal of interest in the field of regenerative medicine due to their biological properties (Hoffman; Dow, 2016; Bajek et al., 2016).

MSCs are undifferentiated, self-renewing adult cells with a high proliferation capacity, giving rise to differentiated and functional cells (Nard, 2007). They have been described to be primarily bone marrow-derived (BMMSCs), but in recent years, adipose-derived MSCs are also being widely studied. These cells have the potential to differentiate into several cell lines and can originate muscle cells, neuronal cells and hepatocytes (Castro-silva *et al*., 2010), among their main mechanisms of action are the secretion of soluble factors that stimulate the migration, mitosis and differentiation of local stem cells, immunomodulation of the microenvironment, in addition to the stimulation of the angiogenesis of the microenvironment, favoring tissue regeneration and repair (Fu *et al*., 2017; Kyurkchiev *et al.,* 2014)

Based on experimental evidence from their preclinical models, Uccelli *et al*. (2011) suggest that MSCs are a promising approach to neural repair and protection, since they have a wide capacity to migrate to injured areas, such as hypoxia, apoptotic or inflamed areas. The potential of MSCs to improve nerve regeneration with morphological and functional recovery, after CNS and peripheral lesions, has been evidenced in several species, such as rodents (Wang *et al*., 2012; Shen *et al*., 2010), non-human primates (Hu *et al*., 2013), pigs (Cho *et al*., 2010) and 3 humans (Braga-Silva *et al*., 2008), however, studies are needed to clarify the therapeutic effect in dogs, since cell therapy can be influenced by the type of cell, the stage of the disease and even the route of administration in the patient.

COMPARATIVE STUDIES AND DIFFERENTIAL DIAGNOSES

The diagnosis of neurologic distemper can be challenging due to the similarity of clinical signs with other neurological diseases, such as immune-mediated meningoencephalitis, central nervous system neoplasms, toxoplasmosis, and neosporosis. Among these, granulomatous meningoencephalitis and necrotizing meningoencephalitis often exhibit clinical symptoms that mimic those of distemper, making it essential to perform complementary tests for an accurate diagnosis. CSF analysis is one of the most reliable methods for this distinction, because in distemper there is a lymphocytic pleocytosis associated with the presence of viral RNA identified by RT-PCR (Józwik and Frymus, 2005).

In addition to cerebrospinal fluid analysis, magnetic resonance imaging is a fundamental tool to differentiate neurological distemper from other diseases that affect

the central nervous system. This examination may reveal alterations typical of distemper virus infection, such as areas of demyelination in the white matter of the brain and spinal cord, especially in regions such as the brainstem and cerebral hemispheres (Beineke et al., 2009). In addition, findings such as hyperintensity on T2-weighted and FLAIR sequences and the presence of meningeal or periventricular enhancement after the administration of contrast medium reinforce the suspicion of the disease (Summers *et al*., 1995).

Magnetic resonance imaging also plays a crucial role in cases where demyelinating encephalitis is suspected, but laboratory tests, such as RT-PCR in the cerebrospinal fluid, show inconclusive results (Shin *et al*., 2004). In addition, this test is essential to differentiate distemper from neoplasms of the central nervous system, such as gliomas and lymphomas, which can cause similar neurological symptoms. In dogs with progressive neurological signs that are refractory to treatment, MRI allows a more detailed evaluation of the extent of the lesions, providing valuable information for defining the prognosis and choosing the most appropriate therapeutic approach (Vandevelde and Zurbriggen, 2005).

CSF evaluation remains an indispensable tool for differential diagnosis, since it can reveal lymphocytic pleocytosis and hyperproteinorrhachia, indicating an active inflammatory process in the central nervous system (Elia *et al*., 2007). The identification of viral RNA in cerebrospinal fluid by RT-PCR is still considered the most accurate technique to confirm infection by the distemper virus, surpassing methods such as direct immunofluorescence (Józwik and Frymus, 2005; Shin *et al*., 2004).

The need for complementary tests, such as magnetic resonance imaging and cerebrospinal fluid analysis, also extends to the differentiation of distemper from other neurological pathologies. Brain tumors can present similar clinical manifestations and, in these cases, imaging tests are essential for the correct distinction. Parasitic diseases, such as toxoplasmosis and neosporosis, can also cause neurological signs in dogs, but they usually respond well to treatment with clindamycin, which aids in clinical differentiation. However, while serological tests are useful to detect antibodies against these agents, RT-PCR in the cerebrospinal fluid stands out as one of the most effective methods to confirm the presence of distemper virus in the central nervous system, allowing a faster and more accurate diagnosis (Shin *et al*., 2004).

Therefore, the combination of laboratory tests, cerebrospinal fluid analysis, and MRI plays an essential role in differentiating neurological distemper from other diseases. The integration of these tools not only improves diagnostic accuracy, but also helps in defining the prognosis and choosing the best therapeutic approach, ensuring a more effective management of the disease.

IMPLICATIONS FOR PUBLIC HEALTH AND EPIDEMIOLOGICAL SURVEILLANCE

Although distemper is not considered a zoonosis, its high rate of spread is an obstacle to veterinary public health. The disease impacts pet dog and wildlife populations, posing a considerable challenge in urban and rural regions with low immunization rates (Harder & Osterhaus, 1997).

Through the analysis of the viral load in the cerebrospinal fluid, it is possible to obtain relevant information about the circulation of more neurovirulent strains and their spread in various canine populations. In addition, effective immunization programs remain the main tactic to control the disease. Research indicates that immunized dogs have a reduced viral load in the Central Nervous System and greater resistance to the advancement of the neurological phase of infection (Greene and Appel, 2006).

FINAL CONSIDERATIONS

The studies analyzed indicate that the viral load in the cerebrospinal fluid is directly correlated with the severity of the neurological manifestations of canine distemper. Dysfunction of the blood-brain barrier, mediated by metalloproteinases and exacerbated inflammatory response, contributes significantly to neuronal damage. The RT-PCR technique has been shown to be the most efficient to confirm CNS infection, contributing to the determination of the prognosis. In addition, the creation of antiviral and immunomodulatory therapies may represent considerable progress in the control of neurological distemper.

However, systematic immunization remains the most efficient tactic to reduce the spread of the virus and reduce the incidence of the neurological variant of the disease. Epidemiological surveillance together with the continuous study of the pathogenesis of CDV are fundamental for the development of new therapeutic and preventive approaches.

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