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How to Determine the Efficacy of Current Methods for the Diagnosis of Canine Distemper Virus?

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ABSTRACT

Canine distemper virus (CDV) is characterized by having an envelope and containing a non-segmented negative single-stranded RNA and belongs to the genus Morbillivirus of the Paramyxoviridae family. This presents multiple cellular tropism, initially replicating in lymphoid tissue to continue in epithelial and neurological tissue. CDV develops a highly contagious disease called canine distemper (CD) that mainly affects dogs and has been known since 1760. DCV infection occurs mainly through direct contact with infected animals or exposure to aerosols; the virus enters the new host via the nose or mouth. The main manifestations of the disease are respiratory and gastrointestinal, advancing to neurological ones. Its diagnosis requires complementing diagnostic methods to reach the definitive one since none is 100% confirmatory, it could be confused with other viral diseases or obtain false negatives/positives. However, the reverse transcription-associated Polymerase Chain Reaction (RT-PCR) technique is currently becoming the standard diagnostic method. Treatment will depend on the signs presented in the disease and is based on supportive care when it is a systemic disease. For respiratory and gastrointestinal presentation, the use of broad-spectrum antibiotics is suggested, in addition to correcting dehydration if present. This guide focuses on the current diagnostic methods of CDV; conducting research and comparison on these would simplify the way of approaching the clinical picture. By comparing and identifying the different methods, information is quickly obtained and the implementation of different diagnostic techniques will be encouraged.

Abbreviations: CDV: Canine Distemper Virus; CD: Canine Distemper; RT-PCR: Reverse Transcription associated Polymerase Chain Reaction; RNP: Ribonucleoprotein Complex; DIF: Direct Immunofluorescence; IHC: Immunohistochemistry; CSF: Cerebrospinal Fluid; IC: Immunochromatography

Background

Canine distemper (CD) is considered a highly contagious acute febrile disease that mainly affects canines and has been known since 1760 [1]. Contagion is mainly direct through contact with the infected animal or through exposure to aerosol, the virus enters the body of the new host orally or nasally and immediately begins to replicate in lymphoid tissues [2]. The clinical signs depend on the virus strain, the host's immune status, the host's age, and the stress levels present. It is estimated that 50% of presentations are subclinical and do not require medical assistance. When the signs are mainly respiratory, a productive cough may be evident, followed by bronchitis and interstitial pneumonia. Gastrointestinal signs are vomiting and watery diarrhea. The duration and complication of the condition is variable and depends on secondary bacterial infections [1]. Regarding the neurological picture, signs can appear weeks or even months after systemic infection, they could appear even without a history of systemic disease. It can be acute or chronic and is always progressive. Multifocal signs usually occur, especially vestibular, cerebellar, and seizures, which can be generalized or partial [3]. The direct action of viral activity on the central nervous system causes encephalitis, which occurs in the early stages of infection in puppies and immunocompromised animals. The virus causes multifocal lesions in both gray matter and white matter. In the gray matter, neuronal infection and necrosis can be observed that can end in polioencephalomalacia [4].

The Virus

Canine distemper virus (CDV) belongs to the *Morbillivirus* genus of the *Paramyxoviridae* family, it is the etiological agent of CD and has multiple cellular tropism, including epithelial, lymphoid and neurological cells. Due to this, a systemic infection is generated which can result in respiratory, digestive, urinary, lymphatic, skin, skeletal and

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central nervous system diseases [5]. CDV is an enveloped virus containing a non-segmented negative single-stranded RNA [2]. All the proteins it encodes have a specific function related to replication and viral cycle, the nucleocapsid (N) encapsulates the viral RNA, serves as a template for the transcription and replication of the two proteins associated with the transcriptase (L and P). The N, L and P proteins together with the viral RNA form the ribonucleoprotein complex (RNP). The CDV envelope is composed of two integral membrane proteins; the fusion protein F and hemagglutinin H, and finally an M protein [5]. Like other viruses of the *Paramyxoviridae* family, glycoprotein H is key because the virus uses it to bind to the host cell receptors in the early processes of infection. After binding, the fusion protein F is what promotes the fusion of cell membranes with the viral envelope, in addition to promoting the formation of syncytia [2]. Various phylogenetic studies have been carried out based on the complete sequence of the H gene of various CDV strains in different geographical locations to infer its genetic diversity. As of 2019, 17 different genotypes have been identified: America 1 (includes almost all commercially available vaccine strains), America 2 to 5, Arctic, Rockborn Type, Asia 1 to 4, Africa 1 and 2, European Wildlife, Europe/South America 1, South America 2 and 3 [5].

Vaccination

The use of modified live virus vaccines since 1950 and their widespread use has considerably helped to keep the disease under control [6]. Sporadic cases and outbreaks of the disease have been reported in vaccinated animals, which may be related to the use of inappropriate vaccines, however, indicating that attention needs to be paid to the emergence of new CDV variants that are diverse enough to prevent currently available vaccines from providing immune protection [7]. Analysis of the H gene sequence has shown that there is a CDV gene that gives rise to 11 different lineages from different geographical regions; the current vaccine strains only contain 2 of these lineages [7].

Diagnosis

The definitive diagnosis is achieved by demonstrating the viral antigen, through PCR in its version that uses prior retrotranscription (RT-PCR) or antigen detection by direct immunofluorescence (DIF) or immunohistochemistry (IHC) [3]. RT-PCR is becoming the standard diagnostic method, but the distinction between field and vaccine viruses requires specific RT-PCRs that are not routinely available [1]. These tests can be performed using conjunctival swabs, blood mononuclear cells, urine, or any tissue sample that includes epithelium. RT-PCR results may be altered by recent inoculation of modified live vaccines [1]. In terms of sensitivity, RT-PCR detected DCV RNA in 88-86% of the samples in the Frisk study [8]. In addition to presenting a high specificity since, in Elia's study, the negative controls were not erroneously detected [9]. IHC or IFD demonstrate the presence of viruses in different tissues, together with histopathology helps to confirm viral infection [1,10]. However, the results of Józwik's study suggest that the sensitivity of immunofluorescence is 50% lower compared to nested PCR. [11]. IFD for DCV antigen usually yields positive samples, however, it can present false negatives, especially in strictly neurological cases because the samples taken are generally conjunctiva or skin [3].

In these cases, the analysis of cerebrospinal fluid (CSF) allows evidence of the presence of the intrathecal virus and relates the signs. It is indicated for any neurological case with multifocal location that does not have intracranial hypertension. In the acute phase of the disease, no significant changes are seen. As it progresses, a mild to moderate lymphocytic pleocytosis can be observed and is associated with the production of intrathecal immunoglobulins. However, this can be seen in other viral infections, it is not specific to distemper. Therefore, other antigen detection methods such as RT-PCR, IFD and/or antibody titers are used. Antibodies in CSF are produced locally, so they are not present in that compartment when there is systemic disease or in vaccinated animals [3]. As for immunochromatography (IC), it can demonstrate viral antigens obtained from conjunctival swabs, vaginal swabs, tracheal washings or urinary sediment. This diagnostic method detects the fusion protein F, the sample upon contact with the antigens solubilizes and forms immune complexes, if it is positive, a pink stripe is evident in the detection zone, if it is negative, a blue stripe is evident. Another study showed that the test compared to nested PCR presents between 89.7% and 85.7% sensitivity and 94.6% and 100% specificity when the samples are blood and nasal lymphocytes respectively [12]. Since the IC test is simple enough to be used by dog owners, it could contribute to early detection to implement treatment and quarantine quickly and thus decrease CDV-related morbidity and mortality [12].

Treatment

Treatment of CD is based on supportive care and requires intensive nursing care, fluid replacement, systemic vascular support, nutrition, and treatment or prevention of secondary bacterial infections [13]. Prudent use of broad-spectrum antibiotics is recommended for the treatment of respiratory signs. Viral pneumonia is often accompanied by secondary bacterial infections, or primary bacterial pneumonia may occur due to immunosuppression caused by DCV [13]. When signs are gastrointestinal, broad-spectrum parenteral antibiotic therapy is essential. Replacement therapy, antiemetics, and nutritional support should also be considered if necessary [13]. In the neurological treatment of CD, the use of allogeneic mesenchymal stem cells obtained from cell banks is possible. The animals that underwent this therapy, had fewer myoclonus and improved their walking ability. However, it is noted that it is necessary to continue studying this type of treatment to better understand the mode of action, determine dosage and schedule [14]. The aim of this work is to determine the effectiveness of current diagnostic methods for detecting CDV in dogs, through a systematic review, with special emphasis in Determine the diagnostic techniques currently used for the detection of CDV and define the three most effective diagnostic methods.

Materials and Methods

This work determines the best diagnostic method for detecting cCDV through a systematic review of the scientific literature published in Veterinary Sciences. The PRISMA declaration [15] guidelines for the proper conduct of systematic reviews are followed. The production process is detailed in its various phases below.

Eligibility Criteria

Regarding inclusion criteria, documents will be considered that address key aspects for the topic of the monograph (diagnostic techniques, data useful for comparison, effectiveness, limitations, advantages and disadvantages), that have been published between the years 2014 and 2024, both inclusive, from recognized academic sources, that present solid scientific evidence and that contain complete information to be cited.

Exclusion Criteria

The exclusion criteria will discard documents that refer to the same study, duplicate documents, documents that are not related to the topic of the monograph, documents that are not published in mentioned sources, with outdated information or with incomplete studies.

Information Sources

The information will be obtained from scientific journals and repositories related to the topic of study, obtained from electronic libraries and from existing universities, theses and reports from undergraduate and graduate degrees from different national and international universities in relation to the study of the CDV, articles from scientific journals and web platforms recognized in the scientific field such as Science Direct, Scielo, Google Scholar, PubMed, ResearchGate, Wiley Online Library, Dialnet, Taylor & Francis and BioMed Central.

Search Strategy

The information necessary to carry out this study will be obtained from various bibliographic sources and for its search key concepts will be used in both Spanish and English such as: Canine Distemper Virus/CDV, Veterinary Virology, Canine Infectious Diseases, Canine Distemper, CDV AND Diagnosis.

Study Selection Process

Initially, a quick review of the titles and abstracts of each study will be done to discard those that do not meet the inclusion criteria. The texts that have been selected will be reviewed in full and must meet both the inclusion and exclusion criteria. A limited number of studies will be included, sufficient to robustly support the conclusions. The final amount will depend on covering all the key aspects of the topic. High-quality studies that meet the specified criteria and evaluations will be prioritized. The Rayyan software tool will be used to eliminate duplicate studies and to organize them during selection.

Data Extraction Process

Data extraction will be carried out independently using a standardized extraction table of our own development. Four variables of interest will be included that will help compare the different diagnostic methods.

List of Data

Outcomes are understood as the specific results that will be evaluated to answer the research question. The primary outcomes will be the sensitivity and specificity of the different diagnostic methods evaluated for the detection of CDV, and the secondary outcomes will include their speed and cost. Data on these outcomes will be sought at all available time points. Other variables: In addition to the outcomes, data will be collected on the characteristics of the participants (age and vaccination status), characteristics of the diagnostic method (type of sample) and the context of the study (country and year of publication).

Assessment of Risk of Bias of Individual Studies

To evaluate the risk of bias of individual studies, the JBI Critical Appraisal Checklist for Precision Studies of Diagnostic Tests will be used, which is a qualitative evaluation of the reviews and depending on the results they will be evaluated individually as high, moderate or low risk of bias [16].

Effect Measures

For the sensitivity outcome, the effect measure to be used will be the proportion of true positives over the total number of patients; For specificity, the measure will be the proportion of true negatives out of the total number of healthy individuals; speed will be measured with the average time to obtain results; and the cost will be evaluated through the average cost per diagnostic test.

Synthesis Methods

To compare the results of each study, the primary and secondary outcomes (sensitivity, specificity, speed and cost) will be tabulated so that they can be analyzed together. From this tabulation, a qualitative analysis of the outcomes will be carried out in a general way. This will allow us to identify the diagnostic methods with the best results. To evaluate the sensitivity and specificity of each study, if the values are not presented directly, the following formulas will be used for Sensitivity: True positives / (True positives + False negatives); Specificity: True negatives / (True negatives + False positives).

Evaluating Publication Bias

To reduce publication bias, information will be sought not only in articles from conventional scientific journals, but also in theses, university degree theses and clinical trials not published in scientific journals. It will be assumed that if all the results found are positive, there is a possibility that publication bias alters the results found.

Evaluating the Certainty of the Evidence

The quality of the evidence will be evaluated using the GRADE method separately for each of the outcomes. This system classifies the quality of the evidence into 4 grades: high, moderate, low and very low. It is considered high when there is high confidence that the true effect is close to the estimate of the effect, and very low when the true effect is substantially different from the estimated effect. Different factors will decrease or increase the quality of evidence for the outcomes; once the quality has been evaluated, an overall classification of the evidence will be obtained [17].

Discussion

By following this methodology, which involves Boolean operators in search engines such as PubMed, Science Direct, Scielo, ResearchGate, Google Scholar, Wiley Online Library, Dialnet, Taylor & Francis, BioMed Central and others, it will be possible to determine the best method for detecting CDV. Time has inexorably passed, and in terms of sensitivity and specificity, RT-PCR and its variants have emerged as the most widely accepted method worldwide.

Conclusion

Kary Mullis's [18] fantastic idea, modified for the detection of viruses with RNA genomes, has long been a reality. Although the methodology involved in performing RT-PCR is still expensive, every effort should be made to implement a definitive technique for the benefit of animals, especially those in danger of extinction. Obviously, the described methodology can be applied to any other viral pathogen as a detection target, since viruses are viruses.

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Conflict of Interest

None.

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