GENERAL ASPECTS OF DISTEMPER: LITERATURE REVIEW

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ABSTRACT

Morbillivirus has single-stranded, negative-sense RNA and does not have the reverse transcriptase enzyme, and is therefore not a retrovirus. Systemic infection with Morbillivirus can be found in wild canids, procyonids such as raccoons, kinkajous, bears, mustelids, hyenas, big cats, domestic cats, cetaceans, non-human primates, and humans. The great ability of Morbillivirus to cross barriers between species is due to mutations in the H protein of the lipoprotein envelope, making it a pantropic virus. Outbreaks of diseases caused by Morbillivirus have been recorded in different species in the same period of time, because in addition to the high virulence, contaminated animals are reservoirs of the disease and intraspecies and interspecies transmission agents. This characteristic of Morbillivirus makes it difficult to eradicate CCV (distemper virus) infections, although there are vaccines for some affected species. The study of Morbillivirus interactions with different species leads us to discuss the concepts of 'One World One Health', 'One Medicine' and 'One Health', as they correlate with the risks to human and animal health that Morbillivirus represents. The epidemiological surveillance work of the VCC is significantly important because it is an emerging infectious disease that poses a threat to the health of humans and animals. Some studies point out that the measles virus is derived from the distemper virus or the rinderpest virus. This study is a complicated of articles published in the literature, which provide information about the pathological mechanisms used by Morbillivirus to infect the host and brain structures with the description of the lesions. In addition, the present literature review addresses the epidemiology, etiopathogenesis, histological alterations, clinical and laboratory diagnosis of distemper.

Keywords: Morbillivirus. Distemper. Epidemiology of Distemper.

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INTRODUCTION

Distemper is caused by a multi-host pathogen, *canine Morbillivirus* of the *Paramyxoviridae family*, responsible for causing severe immunosuppression and neurological disease associated with demyelination (ANDERSON et al., 2012; LIU et al., 2016). About 30% of dogs infected with *Morbillivirus* develop neurological syndromes after one to six weeks from the onset of clinical signs. Puppies aged 3 to 6 months can develop polyencephalopathies with dysfunctions in the proencephalon (GREEN et al., 2020).

The CCV (distemper virus) is a single-stranded, unsegmented, enveloped RNA virus of the *Paramyxoviridae family,* genus *Morbillivirus,* the same genus as human measles (VANDEVELDE & ZURBRIGGEN, 2005). *Morbilliviruses* have already caused epidemics in several species, since these diseases have similar characteristics with signs whose severity varies from subclinical manifestations to chronic brain degeneration, which can lead to the animal's death (UHL et al,. 2019).

Morbilliviruses can cause acute and progressive neurological diseases affecting the gray matter and white matter. These signs include partial or generalized seizures, myoclonus, paresis, paralysis, proprioceptive deficits, circular movements, behavioral changes, vestibular dysfunction, leading to the patient's death or generating chronic neurological sequelae (VON RÜDEN et al., 2021).

Dogs with distemper have a pattern of neurological alterations that resemble human diseases such as Alzheimer's, multiple sclerosis, leukodystrophies, lysosomal enzyme deficiency, epilepsy, cortical malformations (lissencephaly, polymicrogyria), dementia, focal lesions, among others (DATTA et al., 2012).

The anatomopathology model of distemper is the basis for studies on multiple sclerosis because it resembles the mechanism of demyelination. Demyelination is related to the action of the virus on different types of cells. Brain homeostasis is maintained by astrocyte-astrocyte and astrocyte-oligodendrocyte junctions. Changes in these gap junctions can trigger seizures in chronic cases (VON RÜDEN et al., 2017).

Considering that modifications in microglial cells alter brain nutrition, support, and defense mechanisms, the study of the neuropathogenesis of distemper can help to unravel the main consequences of neuroinflammation and how microglial lesions participate in the worsening of brain lesions.

MATERIAL AND METHODS

SYSTEMATIC REVIEW

The systematic literature review was performed in the Google Scholar, Medline, and Pubmed databases in order to obtain an in-depth view of the relevant studies available in the literature.

The following keywords were used to carry out this systematic review: etiology of distemper, distemper general aspects, neuropathogenesis, morbillivirus and anatomopathogenesis. The articles considered in this review were published in the last 40 years, prioritizing the most recent studies of the last 10 years.

Older studies were also used because they provided the first definitions of the characteristics of the disease under study.

The research bases indicated 254 articles, from which 88 publications were selected, in English, Spanish and Portuguese that provided detailed information about the neuropathogenesis of distemper.

After reading the studies, other bibliographies were included, such as veterinary anatomy books.

INCLUSION CRITERIA

The studies published on the general aspects of distemper that met the following criteria were systematic reviews, meta-analysis and scientific articles, as they are studies that provide scientific evidence and show the differences between the studies.

EXCLUSION CRITERIA

Published articles that did not describe or did not address in detail relevant information about the general aspects of distemper were not included in this study.

LITERATURE REVIEW

EPIDEMIOLOGY

Distemper is a highly contagious viral disease that affects carnivores of the Canidae, Mustelidae, Felidae and Procyonidae families in different countries of the world, such as the United States, Finland, Germany, Poland and the countries of the African continent. Wild animals such as foxes, ferrets, and non-human primates can also be affected by *Morbillivirus* (ATHANASIOU et al., 2017).

The seroprevalence of distemper in fox populations ranges from 4 to 17%, but this value may be underestimated due to the high mortality rates in this species that acts as a

reservoir of the disease (BILLINIS et al., 2013). The fatality rate of distemper is 5 to 30% in primates, and the main cause of death is pneumonia followed by neurological changes (VRIES et al., 2014). In a study carried out over seven years, it was observed that the prevalence of distemper in wild dogs in Africa was 16%, compared to 48% prevalence in domestic dogs (WOODROFFE et al., 2012).

Other viruses are related to the distemper virus, such as the human measles virus and the rinderpest virus. *Morbilliviruses* also affect species such as cetaceans, felines, bats, and rodents (UHL et al,. 2019; PFEFFERMANN et al., 2018). Several studies have reported that the distemper virus has a common ancestor and that it has adapted to a variety of hosts over time (VRIES et al., 2014).

Outbreaks caused by CCV have already occurred in several species, such as domestic dogs (*Canis familiaris*), African wild dogs (*Lycaon pictus*), black-footed ferrets (*Mustela nigripes*), Baikal seals (*Pusa sibirica*), African lions (*Panthera leo*) and the spotted hyena (*Crocuta crocuta*) (NIKOLIN et al., 2012).

In 1991 and 1992, CCV infections occurred in captive leopards (Panthera pardus), tigers (Panthera tigris), lions (Panthera leo) and a jaguar (Panthera onca) in North America. There were 17 deaths of these animals, and raccoons were considered the source of infection. In addition to these cats, two black leopards died at the Naibi Zoo, Coal Valley, Illinois, and 2 tigers died at the Shambala Reserve, Acton, California (APPEL et al., 1994). In 1994 approximately one-third of the lion population in the Serengeti, northern Tanzania, died from infections attributed to CCV. There have also been outbreaks in free-living cats such as lynx, Canadian lynx, Eurasian lynx, the critically endangered Iberian lynx and the Amur tiger (NIKOLIN et al., 2012).

The clinical signs found in these species were anorexia, gastrointestinal disease, respiratory disease, and seizures. The CCV was isolated through monoclonal antibody tests that identified the CCV of 3 leopards, 3 tigers and 3 lions that died. Macroscopic and histopathological examinations revealed lesions similar to those found in canids, but there were fewer lesions in the brain and a cell proliferation in the lung with bodies of the disease. Neutralizing antibodies to CCV were found in high titers in the serum of most animals, but were absent or low in some big cats that died after CCV infection (APPEL et al., 1994).

Morbillivirus was identified in domestic cats in China in 2012, the new species called *feline Morbillivirus* (MVFE) caused tubulointerstitial nephritis (MARCACCI et al., 2016). *Morbillivirus* was detected through PCR of urine and blood samples in 12% of stray cats in Italy, cytopathic effects, lysis and syncytial formation in kidney cells were observed.

Histological examination of tissues obtained at necropsy revealed inflammatory infiltrate, degeneration, and tubular necrosis (WOO et al., 2012). In Japan, a study in domestic cats identified the presence of MVFE in the renal tissues of 10 cats with nephritis in 40%. Although the MVFE have genetic diversity, the isolates from Japan and China showed an identical nucleotide sequence, suggesting that there are natural reservoirs. Genetic analysis showed that recombination occurred within the F and H genes (SAKAGUCHI et al., 2015).

In Italy, in a cat with chronic kidney disease (CKD), MVFE was found through urine RT-PCR testing. In 2013, cats with MVFE were recorded in Germany, and recently in Turkey and the United States (USA). Chronic infection caused by *Morbillivirus* may be responsible for viral recombination and heterogeneity. In addition, viral diversity is related to the existence of different viral ancestors involved in the origin of MVFE. In Europe, MVFE has been detected in cats with CKD. Studies show that cats seem to host a heterogeneous population of new paramyxoviruses that are related to CKD in these animals (MARCACCI et al., 2016).

In the VCC, the H protein is the most variable in the *Morbillivirus* genus, which explains a broad spectrum of hosts. The infection can lead to the formation of multinucleated cells, the syncytia. The formation of syncytia is determined by the H protein of the VCC. The cellular receptor for the H protein in host lymphatic cells is the SLAM (signaling lymphocyte activation molecule) molecule that binds to *the Morbillivirus*. SLAM is expressed in humans by memory T cells, B cells, and induced by a range of immune cells, upon activation. The specificity of the VCC H protein and the protein-SLAM receptor interaction represent a potential disseminator of the *Morbillivirus host range* (NIKOLIN et al., 2012).

In humans, the measles virus is a type of *Morbillivirus*. Measles virus and CCV use two cell receptors, CD150 expressed in subsets of cells of the immune systems and nectin-4 expressed in epithelial cells. The measles virus infects immune cells that express CD150, and these cells migrate the draining lymph nodes (SAKAGUCHI et al., 2015). The genus includes the Rinderpest virus (RPV) already eradicated by vaccination, ruminant plague, and distemper virus in dogs. There is evidence of *Morbillivirus* in marine animals, such as cetaceans, this virus being called *Phocid distemper virus-1* (PDV-1) and in felines Morbillivirus has recently been observed, in domestic cats, bat species and rodents (PFEFFERMANN et al., 2018). *Morbilliviruses* were also found in bats, in RT-PCR tests of blood serum, in an incidence rate between 3.3 and 3.1% in a total of 86 bat species, with 4,954 individuals from Brazil, African countries and Europe (DREXLER et al., 2012).

Morbilliviruses are responsible for epidemics that have decimated many populations over centuries, these diseases have similar characteristics among species, with signs whose severity varies from subclinical manifestations to fever, respiratory and gastrointestinal signs, dermatitis and immunosupretion, facilitating immune-mediated bacterial infections, brain damage, spinal cord damage and chronic brain degeneration, which can lead to death (UHL et al,. 2019).

It is estimated that dogs, as reservoirs, can represent a source of infection of the distemper virus for non-domesticated animals. This transmission can pose a threat to wild species populations (COSTA et al., 2019).

Epidemiological studies of the distemper virus, combined with constant epidemiological surveillance, prophylaxis measures such as vaccination, are necessary to contain the spread of the disease from dogs to other species. After rabies, distemper is considered the most relevant disease, due to its severity (COSTA et al., 2019).

Morbilliviruses cause diseases with very high morbidity and mortality in human and animal populations. Outbreaks of measles and rinderpest occurred in the same period in Europe, Asia and Africa between the seventeenth and nineteenth centuries, during these centuries, measles was endemic in Europe. The first record of distemper occurred in Ecuador and Peru in 1735. It can be seen that the occurrence of diseases caused by *Morbillivirus* in different species such as humans, cattle and canines occurred concomitantly on several continents, showing that the distemper virus is pandemic (UHL et al., 2019).

Table 1 shows that a severe measles epidemic occurred at a time when distemper was established in South America and Europe, as well as rinderpest that became endemic on several continents. Historical records of dog outbreaks with distemper in an endemic scenario of measles and rinderpest point to a broad understanding of multihost pathogens, which continuously threaten human and animal populations (UHL et al., 2019).

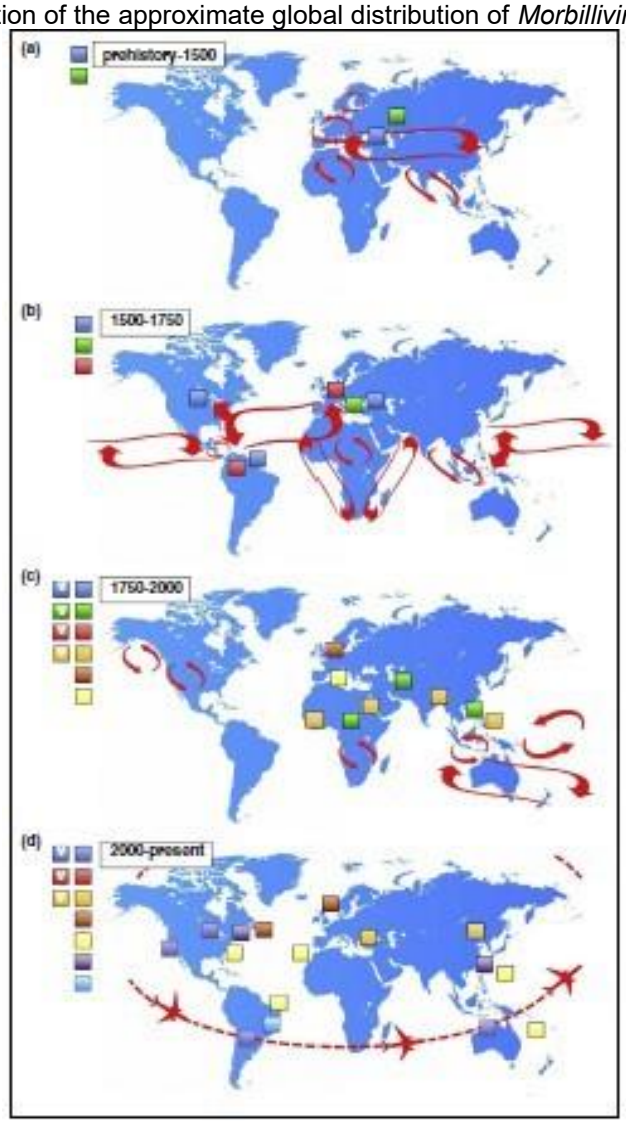
Figure 1 depicts the historical moments in which outbreaks and endemics of diseases caused by *the Morbillivirus occurred,* suggesting that this pathogen originated from a common ancestor and was transmitted to several species. Possibly there was an adaptation of *Morbillivirus* to humans after the first outbreak in animals. The development of resistance in people decreased morbidity and mortality rates. When the occurrence of dogs with distemper was recorded in 1809, similarities with the transmission of measles and greater susceptibility in puppies were noticed. (NAMBULLI et al., 2016).

Table 1: The widespread measles epidemic in the Americas preceded the first canine distemper epizootics between the sixteenth and seventeenth centuries

Sickness	Local	Countries	Century. XVI	Century. XVII	Century. XVIII	Century. XIX
Cinomose	America	Quito, Ecuador, South	NRF	NRF	1748, 1759	NFR
	Europe	England	NRF	NRF		
		France	NRF	NRF	1761-64, 1782-84, 1799	1808
		Germany	NRF	NRF	NRF	1834
		Ireland	NRF	NRF	1761-64	NRF
		Italy	NRF	NRF	1799	NRF
		Russia	NRF	NRF	1771	1820
		Spain	NRF	NRF	1761	NRF
Measles	Americas	Caribbean, Guatemala	1517, 15191523, 1529	NRF	NRF	NRF
		Argentina	1628, 1634-35, 1645	NRF	NRF	NRF
		Ecuador	1558, 15851591, 1597	1611,1612, 1618, 1628, 1634-35,1645	Endemic from 1785	Endemic
		Central America	153134,155963,1576-80	1604, 1613-17	Endemic	Endemic
		Peru	1531-33, 1557-62, 1585-91	16111614, 1618, 1628,1634-35, 1645	Endemic	Endemic
		United States	1533-1533,1592-96	1635, 1657, 1687	1713-1715, 1727,1729, 1739-40,1747,1759, 1772, 1788	1802, 1820, 1837, 1848, 1861-65, 1878-1879, 18831884
	Europe	Canada	NRF	1635, 1687	NRF	1819, 1844, 1846, 1865
		European Union	Endemic	Endemic in 1629–1700, 1665,1675	Endemic 1700, 1800, 1740, 1762, 1751, 1781 1783	Endemic 1808, 1811-1812, 1839, 1846-49, 1882
Rinderpest	America	The entire region				
	Africa	The entire region	NRF	NRF	1726-65	1887-97
	Europe	European Union	1514, 1559, 1598	1609, 1616, 1618, 1625,1665, 1673-74, 1682-83	170922,1726-65, 1769-1800	1887-97, 18001816, 1825-37, 18441863-67, 1877

Source: Modified from UHL et al., 2019.

Figure 1: Representation of the approximate global distribution of *Morbillivirus* throughout history.



(a) *Morbillivirus* (blue) and *Rinderpest morbillivirus* (green) are the oldest *Morbilliviruses* that spread along ancient trade routes (red arrows).
(b) The importation of *Morbillivirus* to the New World and canine distemper virus (red) to the Old World during the Age of Exploration.
(c) Spread of *Rinderpest morbillivirus* to Africa and Asia due to the transboundary movement of livestock and establishment of the first *globally distributed Morbillivirus* . Discovery of ruminant plague (light orange), rinderpest (dark orange), and *Morbillivirus* in cetaceans such as seals, respectively. The development of attenuated vaccines against *Morbillivirus* in different species has brought greater control of the disease in several parts of the world.
(d) The discovery of *feline morbillivirus* (purple), a proposed new member of the genus in Asia and the United States.

Determination of the sequence of *bat Morbillivirus* (light blue with dashed line) from clinical material obtained in Brazil. *Morbillivirus* expands its geographic reach in Asia and Africa and is isolated in Turkey and China. The resurgence of *Morbillivirus* (blue with red line) in regions of the world where they were endemic.

The detection of *Morbillivirus* in cetaceans (yellow) has occurred in a wider range of widely distributed marine mammals. After the eradication of *Rinderpest morbillivirus,* the use of the vaccine in cattle was suspended. *Morbillivirus* remains globally distributed (NAMBULLI et al., 2016).

ETIOPATHOGENY

The *canine Morbillivirus of the* Paramyxoviridae *family* causes severe and highly contagious systemic disease that affects both domestic and wild carnivores (SATO et al., 2012, LOOTS et al., 2017). Infectious diseases in general are the evolutionary result of complex interaction between infectious agents and their hosts, such as adaptation of agents to host cells, specific tropism, neuroinvasiveness, immune response to the virus, specific tropism, among other factors (VANDEVELDE & ZURBRIGGEN, 2005).

The VCC genome is 15,690 nucleotides long and contains six genes. Of these, two are non-structural and six are structural proteins, which are encoded by messenger RNAs (PLATTET et al., 2007). *Morbilliviruses* are encased in lipoprotein envelopes that have an unsegmented negative-sense RNA genome that encodes a single matrix protein associated with the envelope.

The envelope consists of the N nucleoprotein and M protein that is located on the inner surface of the envelope, displaying two surface glycoproteins: the fixation protein (H) and the fusion protein (F). The cellular receptor for the H protein "in vivo" has not been determined. *Morbilliviruses* also have two proteins associated with polymeric RNA (polymerase complex), which are phosphoprotein P and large protein L, and a nucleocapsid protein (N) that encapsulates viral RNA (VANDEVELDE & ZURBRIGGEN, 2005; SATO et al., 2012; LOOTS et al., 2017).

Fusion protein (F) is a classic type I glycoprotein, composed of 662 amino acids essential for viral penetration and dissemination in the host. The translation of the F protein begins at the first codon of initiation, AUG1, or the second codon, AUG61, generating the pre-F0 AUG1 and pre-F0 AUG61, which are translocated to the endoplasmic reticulum and cleaved between amino acids 135 and 136 by a cell signal peptidase, thus producing a peptide of 75 or 135 amino acids, depending on the codon of the translation (VANDEVELDE & ZURBRIGGEN, 2005; SATO et al., 2012; LOOTS et al., 2017).

For membrane fusion to occur, the F protein undergoes a cascade of changes, the F protein represents a potentially active structure of receptor- and hemagglutinin (H)-dependent fusion for the plasma membrane, the F protein undergoes conformational changes, which finally lead to membrane fusion (PLATTET et al., 2017).

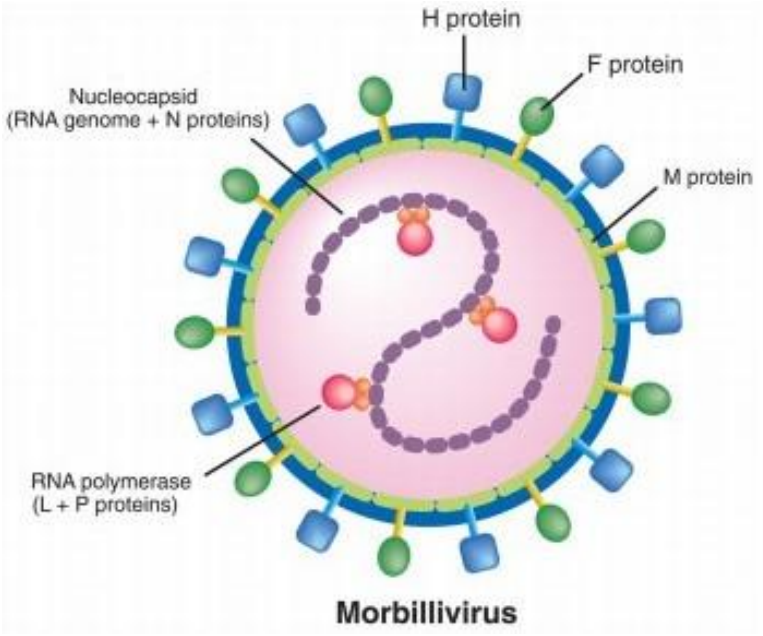
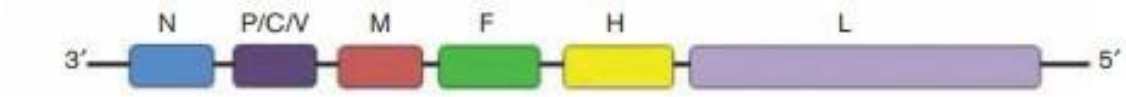


Figure 2



a) The figure shows the viral particle with the lipoprotein envelope, containing the ribonucleoprotein complex consisting of the nucleocapsid. In the envelope, there are M proteins, fusion protein F, and hemagglutinin (H). Viral RNA polymerase contains the L and P proteins (Adapted from SATO et al. 2012 and LOOTS et al., 2017).

b) The two glycoproteins, the hemagglutinin protein (H) (yellow) and the fusion protein (F) (green) together with the large protein L (purple) constitute the ribonucleoprotein complex (RNP) (Adapted from SATO et al. 2012 and LOOTS et al., 2017).

SLAM: THE *MORBILLIVIRUS* RECEPTOR AND THE MECHANISMS OF VIRUS ENTRY INTO THE HOST CELL

SLAM (Membrane Lymphocyte Activation Molecule) acts as a cellular receptor for *Morbillivirus* (FUKUHARA et al., 2019). SLAM is a member of the immunoglobulin superfamily subset and has two extracellular domains (V loop and C2 loop) along with a transmembrane region and a cytoplasmic tail. The interaction between the H protein of *Morbillivirus* and the V domain of the SLAM molecule in target cells is responsible for *Morbillivirus infection* (YADAV et al., 2019).

Morbilliviruses mainly use three types of receptors, which play a role in host specificity and the tropism of viruses in tissues. The signaling lymphocyte activation molecule, SLAM, is the main cellular receptor for viruses in humans, cattle, and dogs, first

identified in humans as the activation receptor of T, B, and B cells induced after activation (YADAV et al., 2019).

Human SLAM is selectively expressed in lymphoid tissues, so human SLAM exhibits tissue tropism. Dogs and cattle have a SLAM molecule homologous to human SLAM that acts as a cellular receptor for VCC and RPV, respectively (TATSUO & YANAGI, 2002).

The mechanisms of entry of *Morbillivirus* into host cells are important to determine its multi-host characteristic and tissue tropism. *Morbilliviruses* have two glycoporteins, hemagglutinin (H) and fusion protein (F) on the viral surface. During the virus invasion, the H protein binds to the host's entry receptor, SLAM, which is also known as CD150. SLAM is an immune cell-specific protein, expressed on the surface of thymocytes, activated lymphocytes, mature dendritic cells, and macrophages (FUKUHARA et al., 2019).

The SLAM receptor is considered a determinant of immunosuppression and induces conformational changes in the F protein, causing the virus to melt to the plasma membrane of the host immune cells. During fusion, some amino acids of the H protein are important to favor the binding of nectin-4 that is expressed on the cell surface, being responsible for the susceptibility of infection by *Morbillivirus* (MESSLING et al., 2005; FUKUHARA et al., 2019).

Figure 3: The 5804PeH strain of the wild-type VCC infects nectin-4-expressing cells in humans and dogs. Members of the VCC and measles virus groups share tropism and common diseases. The study suggests that the abundance of nectin-4 as a VCC receptor on the cell surface is related to its susceptibility to VCC infection. Fluorescence images were captured four days after infection and superimposed with contrasting phases; nectin-4 in the corresponding cell line shaded with IgG; nectin-4, nectin-4-red antibody (NOYCE et al., 2013).

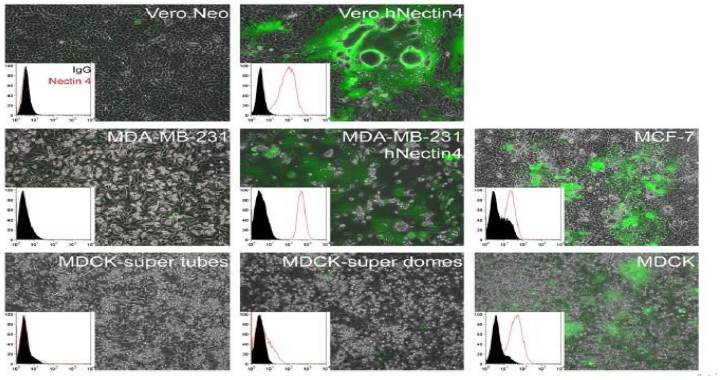
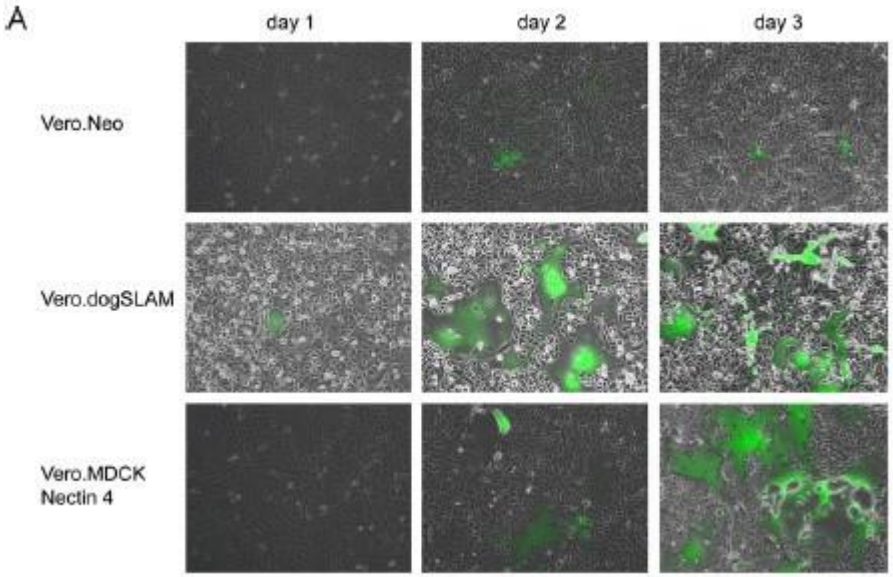


Figure 4: Wild-type CDV5804PeH efficiently infects Vero cells that express dog nectin-4. Canine Vero cells express SLAM. The nectins-4 of the MDCK (canine kidney cells) expressing dog nectin-4 and a plasmid in the control group were infected with the CDV5804PeH strain. Contrast and fluorescence phase: Images were captured and overlaid to visualize the extent of virus replication, with a significant increase in CDV5804PeH. (Adapted from NOYCE et al., 2013).



For many years it was believed that CCV reproduced in the respiratory epithelium before disseminating, but it has recently been concluded that CCV infects macrophages and dendritic cells of the airways using SLAM as a cellular receptor. Infected cells cross the respiratory epithelium and transport the infection to the lymphoid organs, causing viral replication. Nectin-4 is an immunoglobulin, known as the host exit receptor, interacts with high affinity with the viral attachment protein through its distal membrane domain, enabling viral dissemination in the airways. (MÜHLEBACH et al., 2011).

Morbilliviruses infect cells that express CD46 and SLAM, but they also infect other cells through the cell receptor, nectin-4. The cells that express nectin-4 are the epithelial cells, cells of the trachea, bronchi, lungs, oral cavity, pharynx, esophagus, intestines, liver, and urinary bladder. Nectin is a family of adhesion molecules, but only nectin-4 is an epithelial receptor for *Morbillivirus* (YADAV et al., 2019).

Nectin-4 has a transmembrane glycoprotein in its structure with three similar ectodomains, a transmembrane region and a cytoplasmic tail. It is expressed basolaterally in the epithelial cells in the vicinity of infected lymphocytes and dendritic cells and acts as a viral receptor through a mechanism similar to the interaction between SLAM domain V and *Morbillivirus H protein* (YADAV et al., 2019).

SLAM is an efficient receptor for wild VCC in canine tissue cultures. In immunocytochemical analyses, SLAM is expressed in a limited way in the CNS compared to lymphoid tissues, showing that there are probably other viral receptors (VANDEVELDE & ZURBRIGGEN, 2005). The transmission of *Morbillivirus* occurs through aerosols to the

respiratory tract, and the first replication occurs in lymphoid tissues, causing severe long-term immunosuppression (VANDEVELDE & ZURBRIGGEN, 2005; COSTA et al., 2019). The SLAM receptor in the immune system correlates with immunosuppression associated with Morbillivirus-mediated cytolytic infection in lymphoid tissue. Other receptors are responsible for the entry of VCC into nectin-4, as the epithelial cell receptor contributes to *Morbillivirus multitropism*. The SLAM receptor binds to the H protein of the distemper virus in specific regions, which comprise 500 to 550 amino acids (COSTA et al., 2019).

After six days of infection, all lymphatic tissues are affected and viremia is developed (KIM et al., 2001). The incubation period is approximately 1 to 4 weeks, depending on the immune status of the affected dogs (AWAD, 2019). Dogs without antibodies against the distemper virus die in approximately three weeks after infection (KIM et al., 2001).

At the beginning of the infection, the distemper virus invades macrophages, respiratory tract and later affects other organs such as the gastro-intestinal tract, lymphoid organs, urinary bladder and central nervous system. The manifestations can be subclinical to lethal, and the main clinical signs are fever, respiratory, gastrointestinal and dermatological changes (ATHANASIOU et al., 2017).

The depletion of lymphocytes, especially TCD4 cells, due to lymphoid cell apoptosis in the initial phase causes persistent immunosuppression, and secondary bacterial infections may occur. (BEINEKE et al, 2009).

During the acute phase of infection, T cells are more affected than B cells, while CD8+ cells are less affected and recover faster compared to CD4 lymphocytes. After 10 days of infection, CCV replicates through epithelial tissues, causing multisystem involvement in the respiratory tract, gastro-intestinal tract, and dermatological changes (BEINEKE et al 2009; VANDEVELDE & ZURBRIGGEN, 2005).

On its way to the CNS, the CCV invades the brain through infected mononuclear cells, circulating through the cerebrospinal fluid (CSF) and fusing with the ependymal lining of the ventricles, causing periventricular and subpial lesions. When it affects the CNS, it determines the neurological syndrome with demyelinating lesions, which can occur within 3 weeks of the onset of infection. Neurological signs can occur in the absence of systemic signs (VANDEVELDE & ZURBRIGGEN, 2005).

The virus can cause damage to the brain, such as demyelinating leukoencephalomyelitis, and to the spinal cord, which induces immune-mediated chronic neurological manifestations, with increasing levels of MHC class II molecules as a result of the virus's permanence in nervous tissue (BEINEKE et al 2009; KLEMENS et al., 2019; RENDON-MARIN et al. 2019). Demyelination occurs mainly in astrocytes, with hypertrophy

of these cells, isomorphic gliosis, reactive astrocytes (gemiocytes) and, occasionally, the formation of astrocytic syncytial (KLEMENS et al., 2018).

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