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Canine distemper: A fatal disease seeking special intervention

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Abstract
Canine distemper (CD) is acute and highly infectious viral disease. It is caused by single-stranded RNA virus with a lipoprotein envelope, is a Morbillivirus in the family Paramyxoviridae. Its fatality rate is second only to that of rabies affect carnivores and domestic dogs of any breed and age. CD virus can infect a wide range of carnivore's including members of the Canidae, Felidae, Hyaenidae, Mustelidae, Procyonidae, Ursidae, and Viverridae. The lethal infections also have been reported in non-human primates and non-carnivore species demonstrating the remarkable ability of CD pathogen to cross species barriers. The transmission is through aerosol of respiratory exudates containing virus, although other body excretions and secretions can result in infection in susceptible hosts. There is no curative treatment for CD infection. The treatment is mostly supportive and for secondary complication and prevented by vaccination. The CD virus had broad and expanding host range and sustained within wildlife reservoir hosts considerably hampers disease eradication. Animal health care professional including those working with nondomestic carnivores, should be familiar with the transmission, clinical signs, diagnosis, and clinical management of this disease. Awareness about CD diseases should be created and vaccination should be advocated among the people.

Keywords: canine distemper, virus, carnivore, transmission, clinical signs, diagnosis and vaccination

Introduction
Canine distemper (CD) is acute, highly contagious and severe systemic viral disease affecting carnivores and other wild animals worldwide that may manifest with various forms like respiratory forms, central nervous system form, hyperkeratosis (skin form), often generalized infection, or a combination of these. It is a highly contagious viral pathogen, lethal to both wild and domestic, sea and land living animals. The fatality rate is second to that of rabies affect carnivores of any age group [1]. The disease course and pathogenesis in CD resemble to the human measles viral infection including, fever, rash, respiratory signs, lymphopenia, and profound immunosuppression with generalized depletion of lymphoid organs during the acute disease phase [2] and shows a high incidence of neurological complications [3]. CD virus can infect a wide range of carnivore including members of the Canidae, Procyonidae, and Mustelidae. CD is still very common in young unvaccinated dogs, usually in their early life, but many cases are also seen in adults [4]. CD virus represents a rather promiscuous agent causing distemper like pathology in a variety of different carnivore including members of the Canidae, Procyonidae, and Mustelidae and also non-carnivorous species [5, 6].

CD initially diagnosed as a life-threatening disease in domestic dogs, but latter on it has subsequently been recognized as wide range of hosts including some non-human primates, posing a great risk for conservation of several domestic and wild animals [5, 7]. However, morbidity and mortality may vary greatly among different species of animals [8]. CD develop pneumonia, conjunctivitis, rhinitis, and tracheitis. The lungs are typically edematous, and microscopically there is broncho-interstitial pneumonia with necrosis of the epithelium lining the small airways and thickening of the alveolar walls [9]. There is no specific treatment for CD disease and prevented by vaccination [5]. Switching to different host capability of CD virus is the grave concerns and extinction threat it poses to several endangered wildlife species [10, 11, 12]. These CD virus can affect the viability of animal's population both directly through effects on host's survivability and reproduction but also indirectly by altering their behavior, movement pattersns, social system and community structure [13]. The present article is intended to provide an insight on etiology, transmission, host range, pathogenesis, clinical signs, diagnosis and prevention of CD virus in different species.

Etiology

Canine distemper virus is the large single stranded RNA virus caused by Morbilli virus [14]. Morbilli virus belong to the family Paramyxoviridae [14] and include a number of highly pathogenic viruses, such as measles virus, rinderpest virus, CD virus, and peste-des-petits-ruminants virus, which cause devastating diseases in humans and animals [15,16]. The CD virus is an enveloped, negative-sense, single-stranded RNA virus. The virus contains six structural proteins called nucleocapsid, phospho, large, matrix, hemagglutinin and fusion protein, and two accessory non-structural proteins that were found as extra transcriptional units within the P gene [17]. The affinity of virus towards different cells types is the matter of concern which make the disease very pathogenic in canine and others. CD virus exhibits lymphotropism, neurotropism and epitheliotropism resulting in systemic infection of almost all organ systems including digestive, respiratory, urinary, lymphatic, endocrine, cutaneous, skeletal, and central nervous system [3, 18, 19]. Phylogenetic and molecular evolutionary analyses of CD virus have revealed that mutations affecting the binding site of the haemagglutinin protein for virus entry receptors called as Signaling Lymphocyte Activation Molecule (SLAM), also known as CD150 and Poliovirus Receptor Like-4 (VRL4), also known as nectin-4 are associated with the occurrence of disease emergence in novel host species [20, 21, 22, 23, 24].

Transmission

The CD virus is relative fragile in the environment close contact is require between affected and susceptible for horizontal transmission of virus. The virus can survive at lower temperatures (e.g, 48 hr at 25^0C and 14 days at 5^0C). Virus also transmitted either by direct contact or by fomites [25]. Transplacental transmission has been reported in domestic dogs [26]. It has been reported that during acute phase of infection, the excretions and secretions from infected animals contains the virus [27, 28], and even during sub-clinically infected animals virus shedding may follow for up to 90 days [27]. Therefore, the CD is readily transmitted to new hosts through contact or aerosolized, oral, respiratory and ocular fluids and exudates containing the pathogen [29]. It produces clinical manifestation such as fever, serous nasal discharge, and cough, as well as respiratory and gastrointestinal signs often complicated by secondary bacterial infections. Furthermore, the most notorious property of Morbillivirus infection is the establishing of severe transitory immunosuppression [30, 31].

Host Range

CD virus is a worldwide distribution that occurs in all members of the Canidae, Mustelidae, and Procyonidae families [32]. Domestic dogs have been considered as reservoirs of infection for wild carnivores [33, 34, 35, 36, 37]. The CD viral infection has been reported in many mammalian family *viz.* Canidae family, Felidae (wild cats), Hyaenidae (hyaenas), Mustelidae (weasel-like carnivores), Procyonidae (raccoon-like carnivores), Ailuridae (red pandas), Ursidae (bears), non-human primates (rhesus monkey) and Viverridae (civet-like carnivores) [5, 38, 39, 40]. Mortality among varies species depends mainly on host immune status, approximately 25-75% of infected animals often survive among canids. In mustelids, procyonids, and red pandas, the rate of mortality is much higher than canines [5, 38]. Infections in non-human primates like rhesus monkey (Macaca mulatta) and cynomolgus macaques have raised several concerns of a potential zoonotic risk of CD virus in humans. For wild or captive animals *viz.* lions, tigers, red pandas, and leopards, a very few cases of canine distemper were reported in India. However, CD is prevalent among dogs in India [41] and it's often poses a threat of CD virus transmission to wildlife [12]. Other wildlife species also could play a role in maintenance and transmission of CD virus [12]. Clinical CD cases has most commonly been documented in red pandas and giant pandas [42, 43, 44, 45, 46]. The disease has been also reported in Asian elephants (Elephas Maximus) [47].

Clinical signs

The clinical signs in individuals are highly variable and it may depend on affected species, virus strain, immunological status, environmental conditions and host age. For instance, in ferrets the mortality may reach up to 100% [48]. In wild animals the clinical signs are generally similar to those reported in domestic dogs. However, the severity and the outcome of the infection may vary greatly among different species the signs of CD virus infection in wild animals are often subtle and rarely observed [28]. CD virus infection with weak immune response in animals leads in non-specific signs such as listlessness, appetite loss and fever. If a strong immune response develops in affected host, no clinical illness ensues.

Two different clinical forms of CD virus can be observed in animals with minimal or no immune response first is an acute systemic form and second is a chronic nervous form [49]. Acute systemic disease occurs 2-3 weeks post-infection [28]. The virus continues to replicate and spread throughout the body causing severe clinical signs, which include fever, serous nasal discharges that rapidly become mucopurulent, oculonasal discharge, coughing, dyspnoea, pneumonia, depression, anorexia, vomiting and diarrhoea may be with blood [50, 51]. During this stage of infection, the virus is found in every secretion and excretion of the body [48]. Hyperkeratosis of the foot pads (hard pad disease) is also a symptom in wild animals but rare. The central nervous system (CNS) relevant clinical signs may be concurrent or follow systemic disease within 2-3 weeks. Signs are progressive and varied depending on the area of the brain affected but commonly include localized twitching, tremors, ataxia, disorientation, paresis or paralysis beginning in the hindlimbs, epileptiform convulsions characterized by salivation and often chewing movements [52]. Other neurological signs are abnormal behaviour, convulsions or seizures, blindness, cerebellar and vestibular signs, paresis or paralysis, inco-ordination and circling [28, 53]. The animals with demyelinization of neurons lesion may die within 2-4 weeks after infection [51, 54]. The clinical signs of CD viral infection are often exacerbated by secondary bacterial infections [27].

In domestic dogs around 50-70% of CD virus infections cases are thought to be subclinical type [55]. CD virus can persist for longer periods of time in the neurons, uvea, urothelium and skin. It causes hyperkeratosis in skin, most common in domestic dogs, even after host responded with strong immunity against infection [29, 56, 57]. CD virus can infect tooth buds and ameloblasts causing clear enamel hypoplasia, once infection occurs before the eruption of permanent dentition [58, 59]. The mortality rates due to CD virus infection vary among susceptible species [52] and could be as high as 100% in ferrets [60].

Other than canines

CD has been reported often in wild felids [61, 62, 63, 64, 65]. CD has been reported in asian-african lion (*Panthera leo*), tiger (*Panthera tigris*), leopard (*Panthera pardus*), and jaguar (*Panthera onca*) with signs of gastrointestinal, respiratory, and CNS disease. Generalized seizure activity, the most common neurologic abnormality, usually culminated in acute death in felids. Infected animals (lions and tiger) are emaciated and showing neurological symptoms such as seizures, tonic-clonic contractions, falling, inability to rise, and paresis [66]. Beside occulonasal discharge the black footed farrets shows symptoms likes diarrhea, anorexia, seizures, and myoclonus, with often severe hyperkeratosis of the foot pads, erythema and associated pruritis [67, 68]. The fatality rate in the highly susceptible black-footed ferrets and domestic ferrets are close to a 100% [69]. Cystitis with pyuria are common in raccoons [70, 71] and often jaundice is associated with CD viral infection in raccoons [72].

Pathogenesis

CD virus may infect a new host by naso-oral route [56]. CD virus is considered a pantropic cell pathogen that has the ability to infect three different types of cells including epithelial (particularly respiratory and digestive tract mucosa), lymphoid, and neurological cells. There it multiplies in tissue macrophages, infected cells carry the virus to the draining lymph node, where resident activated T-cells and B-cells are infected, resulting in virus amplification and the initiation of primary viremia [73]. This viremia occurs within 24 h, again virus gets disseminated to secondary lymphoid organs, via the lymphatics including the spleen, the thymus, the tonsils and subsequently a systemic spread through the entire immune system resulting in severe immunosuppression [18, 51, 74, 75]. Within 2 to 4 days, other lymphoid tissues become infected, and by day 6, the digestive tract mucosa, Kupffer cells of liver and spleen are infected, that leads into systemic reaction, fever and leukopenia [28, 56]. Further CD virus spread by cell-associated viraemia to other epithelial cells and the CNS [51, 54]. At the end of 6 to 10 days of infection respiratory and gastro-intestine relevant signs are most common, CD virus can infect the epidermal cells of a wide range of species, along with aforesaid sings, and it also induces erythmatous patches (rashes) of different size varying from 3 to 8 mm mostly on neck and face region. An increasing number of patches appear around the mouth while the infection progresses [76, 77]. Furthermore, footpad keratinocytes are commonly infected, and these site possess important role in diagnosis of CD virus through biopsy as viral antigen easily detectable from here [78]. Excretion of virus from infected host begins approximately 1 week after infection [29]. As is believed, for neuro-invasion of CD virus there is different ways may be via infected peripheral blood mononuclear cells (PMBCs) that are transported through the blood brain barrier. Afterwards, there is a virus release that results in the infection of the astrocytes, the microglia, the oligodendrocytes, the neurons, the ependymal cells, the choroid plexus cells [3].

The Signalling Lymphocyte Activation Molecule (SLAM, CD150) and nectin-4 (poliovirus-receptor-like-4) are the two major host cellular receptors that play a critical role in CD virus pathogenesis [79, 80, 81]. Both of these receptors possess an immunoglobulin-like variable domain (V) that provides a binding surface for morbilli viruses [80, 82]. SLAM serves as an immune cell receptor and is expressed on the surface of activated T and B lymphocytes, dendritic cells and macrophages [81, 83]. Out of six structural protein for this receptor, the H protein has the greatest genetic variation and is a key protein in the attachment of the virion to receptors on the host cell surface [84]. The nectin-4 cellular receptor has recently been recognized as the epithelial cell receptor for CD viral [80, 81, 85]. VRL4 (nectin-4) is involved in the cell adhesion, participating in the organization of epithelial and endothelial junctions of host cells [86]. In CD disease, at six to nine days of post infection, the virus enters the epithelial cells of the respiratory, gastro-intestinal, urinary and endocrine system via an epithelial receptor [18, 87], now it known as nectin-4 [85, 88]. CD virus amplification takes place within the epithelial cells, after which the virus is released causing extensive respiratory, intestinal and dermatological symptoms [18, 89]. In a host with a weakened immune response, CD virus will move into the CNS, producing neurological symptoms [75]. As SLAM receptor being under-expressed in the CNS, It has been suggestive that, nectin-4 plays a role in the neurovirulence in CD [3, 81, 90].

Pathology

The most significant gross lesions are broncho-interstitial pneumonia and depletion of lymphopoietic organs, and hyperkeratosis of the nose, foot pads, and eyelids. In uncomplicated CD viral infection, the only consistent pathologic finding is thymic atrophy [52]. Microscopically, bronchioles often contain purulent exudates with focal necrosis and attenuation of bronchiolar epithelium. Alveolar septa are stretched by infiltration of mononuclear cells, and alveolar space may be filled with polymorphonuclear (PMN) cells and fibrin. Intracytoplasmic inclusion bodies most commonly occur, while intranuclear inclusion bodies occasionally, and found in the syncytial giant cells, transitional cells of urinary bladder, CNS and bronchial epithelium. Syncytial giant cells in the lungs and CNS white matter, anterior uvea, and lymph nodes may also be present but may be less evident. While the histopathologic lesions in felids are different, lungs of large felids may show diffuse alveolar type 2 cell hyperplasia with intra cytoplasmic and intranuclear inclusion bodies. This cellular response appears to be unique to large felids [52].

In CD viral infection, white-matter demyelization occur which may be multifocal or patchy, infection often develops first in perivascular macrophages, astrocytes, and choroid plexus epithelium. it became most severe in the cerebellum, periventricular white matter adjacent to the fourth ventricle, rostral medullary velum, optic tracts, and spinal cord. The neutrophil may be vacuolated with loss of myelin and preservation of axons in early lesions. Gray matter lesions may occur in the cerebral cortex, cerebellum, brainstem, or spinal cord. Nuclear or cytoplasmic eosinophilic viral inclusion bodies will be present in astrocytes, other glial cells or neurons. The histopathology of feline brain may lack the typical canine pattern of demyelination with astrocytosis and vascular cuffing. Most cats have had mild, patchy CNS lesions compared with those of canids [52, 91]. Characteristic footpad thickening (hard pad disease) or marked hyperkeratosis is the classical cutaneous CD disease lesion. Hyperkeratotis may be also been seen in the nasal planum or in haired skin but it's not commonly occur in wild animals. Both intracytoplasmic and intranuclear inclusion bodies and syncytial cells may be present in the epidermis. Small numbers of lymphocytes may infiltrate the epithelium. Secondary infection in hyperkeratotic footpad lesions is

commonly encountered in animals that lead into pustular dermatitis dogs [25, 92, 114].

Diagnosis

The CD disease can be diagnosed by observing progression of disease, mortality rate and clinical symptoms of live animals. Along with clinical signs and post mortem examination individuals can reach up to tentative diagnosis for CD. However, this form of diagnosis may remain problematic and difficult due to the many varied clinical presentations of these disease. Laboratory tests are necessary for a confirmative diagnosis and to exclude other diseases with similar clinical manifestations so differential diagnosis should be conducted. Diagnosis of CD viral infection in wildlife is more difficult due to the challenges associated with acquiring and cold storage of samples in the field for further testing in the laboratory. Low numbers of CD viral inclusions may be detected in the cytoplasm (and occasionally nuclei) of stained peripheral blood cells, especially lymphocytes. The inclusion bodies are unlikely to be present in either the blood or conjunctival scrapings outside of the acute phase of infection. Diagnosis is mostly confirmed by post mortem using histopathology and immunological tissue stains although the specificity and sensitivity for the latter are not known for most wildlife species. Increased anti-CD viral antibody in the CSF is definitive evidence of neurologic CD viral infection. Enzyme-linked immune sorbent assays (ELISA) have been developed to detect serum IgG and IgM antibodies to CD virus [18, 94, 95].

Immuno-histocyto-chemistry is also useful in diagnosing CD, Immunofluorescence test (IFT) is usually performed on cytology smears prepared from the conjunctival, tonsillar, genital, respiratory epithelium [91]. One of several techniques that have been developed for the detection of CD virus is the reverse-transcription PCR assay [96, 97, 98], it has been widely used predominantly targeting the highly conserved N gene. While, RT-PCR methods are specific, more sensitive, and rapid method of diagnosis. A more rapid diagnostic technique for the detection of CD virus is real-time RT-PCR [99, 100, 101]. Serological assays to detect and determine specific titers against CD virus are the indirect fluorescent antibody test (IFAT), ELISA and the serum-neutralization test. Both the IFAT and ELISA are used to detect IgM and IgG antibodies against CD virus in domestic dogs and various non-dog hosts. Virus isolation is conducted in pulmonary alveolar macrophages or by co-cultivation of infected tissues with mitogen-stimulated lymphocytes derived from healthy dogs [102] or with the aid of ferret blood lymphocytes [28, 103, 104].

Treatment

The treatment of infectious CD viral diseases is often difficult, especially in wildlife animals. Treatment is commonly based on symptomatic and supportive therapy as there is no specific antiviral drug available for therapeutic use against CD viral infection in any species, including domestic dogs. The main aim is to limit secondary bacterial invasion and controlling neurologic manifestations. Veterinarian should try to give balanced electrolyte solutions, parenteral nutrition, antibiotics, analgesics, antipyretics and anticonvulsants drugs and along with these symptomatic and supportive therapy good nursing care is essential for infected animals [47].

Prevention and control

It might be impossible to eradicate CD virus because of its global distribution and the wide variety of susceptible wildlife species. Even though CD infection is best prevented by vaccination. A variety of vaccines are available against CD for dogs and other domestic and nondomestic animals [5]. Domestic dogs are vaccinated with commercially available vaccines containing the modified live virus. Different type of modified live virus vaccine are available in market and it should be used according to the manufacturers' directions [47]. The standard attenuated virus vaccines should not be used in nondomestic species. Because, some nondomestic species are often more susceptible to CD viral infection than dogs. A recombinant canary-poxvirus vectored vaccine is now available that is safe, does not contain live virus, and cannot cause distemper [105].

Some researcher evaluated an orally available, shelf-stable pan-morbilli virus inhibitor that targets viral polymerase [106]. Other compounds such as fucoidan, a sulfated polysaccharide found in brown algae, have also been evaluated for their ability to act as antiviral drugs against CD virus [107]. Several flavonoids (quercetin/morin/rutin/hesperidin) and phenolic acids (cinnamic/trans-cinnamic/ferulic acids) had ability to inhibit stages of the CD viral replication cycle *in vitro* [108]. The development of some therapeutic strategies at the immune-modulatory level and in reactivating oligo-dendrocytes from a progenitor pool, even in chronically demyelinated lesions of the CNS [109].

The CD virus is very fragile and extremely susceptible to UV light, heat, desiccation, and common disinfectants such as formaldehyde, phenolic compounds, and quaternary ammonium compounds. The CD virus does not survive in the environment for more than a few hours at room temperature. It can survive for at least two weeks in shady environments at near-refrigeration temperatures. Infected animals should be quarantined from other animals for several months due to the possibility of prolonged viral shedding during this time [110]. Transmission is through aerosolization of respiratory exudate containing the virus, although other body excretions and secretions. Therefore, environmental hygiene where dogs kept should be strictly controlled. Emphasis should be given for susceptible groups of animals during control and prevention of CD viral infection in endemic areas. Several challenges associated with wildlife vaccination, animal's health care specialist must consider the safety and efficacy of the vaccine in the specific species, mode of vaccine delivery, administering the required booster shots and finally the cost involved in initiating and implementing a vaccination programme in wildlife [12, 111, 112, 113].

Conclusion

CD is the most important worldwide infectious viral disease of dogs and other carnivores of any age, and its fatality rate is second only to that of rabies. The virus causes a high incidence of mortality and morbidity in young aged and immune compromised animal. The absence of curative therapy and its genetic variation make the CD infection the highest clinical diseases to the wide range of carnivores. CD virus is an emerging pathogen posing a serious threat to the conservation of several captive and free-ranging wildlife populations. Its ability to infect multiple hosts considerably hampers disease eradication. CD infection has no curative

treatment, therefore, to prevent viral infection, vaccination should be advocated in endemic areas.

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