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Cross-species transmission of canine distemper virus—an update

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ABSTRACT

Canine distemper virus (CDV) is a pantropic morbillivirus with a worldwide distribution, which causes fatal disease in dogs. Affected animals develop dyspnea, diarrhea, neurological signs and profound immunosuppression. Systemic CDV infection, resembling distemper in domestic dogs, can be found also in wild canids (e.g. wolves, foxes), procyonids (e.g. raccoons, kinkajous), ailurids (e.g. red pandas), ursids (e.g. black bears, giant pandas), mustelids (e.g. ferrets, minks), viverrids (e.g. civets, genets), hyaenids (e.g. spotted hyenas), and large felids (e.g. lions, tigers). Furthermore, besides infection with the closely related phocine distemper virus, seals can become infected by CDV. In some CDV outbreaks including the mass mortalities among Baikal and Caspian seals and large felids in the Serengeti Park, terrestrial carnivores including dogs and wolves have been suspected as vectors for the infectious agent. In addition, lethal infections have been described in non-carnivore species such as peccaries and non-human primates demonstrating the remarkable ability of the pathogen to cross species barriers. Mutations affecting the CDV H protein required for virus attachment to host-cell receptors are associated with virulence and disease emergence in novel host species. The broad and expanding host range of CDV and its maintenance within wildlife reservoir hosts considerably hampers disease eradication.

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Introduction

Morbilliviruses belong to the family *Paramyxoviridae* and include a number of highly pathogenic viruses, such as measles virus, rinderpest virus, canine distemper virus (CDV), and *peste-des-petits*-ruminants

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virus, which cause devastating diseases in humans and animals. In the last decades, morbilliviruses emerged also as causative agents of several mass-mortalities in marine mammals [1,2]. Canine distemper is a fatal disease of dogs with a worldwide distribution [3]. The causative agent, CDV, is an enveloped, negative-sense, single-stranded RNA virus. Similar to other paramyxoviruses the virus contains six structural proteins, termed nucleocapsid (N), phospho (P), large (L), matrix (M), hemagglutinin (H) and fusion (F) protein, and two accessory non-structural proteins (C and V) that were found as extratranscriptional units within the P gene [4]. Generally, CDV exhibits lympho-, neuro- and epitheliotropism resulting in systemic infection of almost all organ systems including respiratory, digestive, urinary, lymphatic, endocrine, cutaneous, skeletal and central nervous system (CNS) [5,6]. The disease course and pathogenesis in canine distemper resemble those of human measles virus infection including, fever, rash, respiratory signs, lymphopenia, and profound immunosuppression with generalized depletion of lymphoid organs during the acute disease phase [7]. In addition, CDV infection shows a high incidence of neurological complications [5].

Unlike the related measles virus which is maintained by single host species, CDV represents a rather promiscuous agent causing distemper-like pathology in a variety of different carnivorous and also non-carnivorous species [8–10]. Clinical findings and pathology resemble largely the disease in dogs. However, morbidity and mortality may vary greatly among animal species. Phylogenetic and molecular evolutionary analyses of CDV have revealed that mutations affecting the binding site of the H protein for virus entry receptors (*signaling lymphocytic activation molecule* [SLAM, CD150] and nectin-4) are associated with the occurrence of disease emergence in novel host species [11–15].

The aim of the present article is to give an updated overview of interspecies transmission of CDV and the pathogenesis of distemper in different mammalian species.

Distemper in carnivore species

Domestic dogs

The pathogenesis of CDV infection in domestic dogs has been extensively reviewed previously [3,5]. In brief, disease duration and severity in domestic dogs depends mainly on the animal's age and immune status and strain virulence. The primary mode of infection is via inhalation [16]. Initially, CDV replicates in lymphoid tissue of the upper respiratory tract. Here, monocytes and macrophages are the first target cells which propagate the virus [17]. Following a variable incubation period (one to four weeks), animals develop a characteristic biphasic fever [16,18]. During the first viremic phase, generalized infection of lymphoid tissues with lymphoid depletion, lymphopenia and transient fever is observed. Profound immunosuppression is a consequence of leukocyte necrosis, apoptosis and dysfunction [16,19,20]. Second viremia is associated with high fever and infection of parenchymal tissues such as the respiratory tract, digestive tract, skin, and CNS [16,17]. During this disease stage, various clinical manifestations may be present such as conjunctivitis, nasal discharge, anorexia, respiratory signs, gastrointestinal signs, and neurological deficiencies [16]. Respiratory signs are a sequel of virus-induced rhinitis and interstitial pneumonia, while vomiting, diarrhea and dehydration are caused by gastrointestinal tract infection [21]. Often enteric and respiratory signs are worsened by secondary bacterial infections. Characteristic dermal manifestations include pustular dermatitis (distemper exanthema) and hyperkeratosis of foodpads and nasal planum (hard pad disease). In young animals also enamel hypoplasia and metaphyseal osteosclerosis have been described following CDV infection [22]. Neurologic signs depend on viral distribution in the CNS and include hyperesthesia, cervical rigidity, seizures, cerebellar and vestibular signs, as well as paraparesis or tetraparesis with sensory ataxia [9,23]. Histological manifestations include polioencephalitis and demyelinating leukoencephalomyelitis [24,25]. Recovery depends on the host immune response. Particularly, a strong and effective cellular immune response can eliminate the virus prior to infection of parenchymal tissues, while weak and delayed cellular and humoral immune responses lead to virus spread and persistence, respectively [5,16,26].

Wild canids

Besides domesticated dogs natural and/or vaccine-induced CDV-associated disease has been reported in almost all genera of the tribus true canids. Affected members of the genus Canis include Australian dingos (*Canis dingo*) [27], coyotes (*Canis latrans*) [28,29], black-backed jackals (*Canis mesomelas*) [30], golden jackals (*Canis aureus*) [31], Canadian wolves (*Canis lupus*) [32], American gray wolves (*Canis lupus*) [33], Mexican wolves (*Canis lupus baileyi*) [34], Iberian wolves (*Canis lupus*) [35], and Apennine wolves (*Canis lupus*) [36]. Phylogenetic analyses suggest a CDV spillover from domestic dogs to free-ranging jackals and wolves [30,35]. Referring to this, sequencing of CDV from Apennine wolves in Italy identified a strain belonging to the Arctic lineage, known to circulate in European dog populations [36]. The Ethiopian wolf (*Canis simensis*) is recognized as the rarest canid species in the world and the most threatened carnivore in Africa. This species is almost extinct due to combined effects of rabies and CDV infections [37]. Wolf-derived CDV from the Ethiopian outbreak show sequence homologies to isolates from domestic dogs in the USA, Germany and Japan, suggestive of global virus spread [37]. There is serological evidence of CDV exposition to maned wolves (*Chrysocyon brachyurus*) in Brazil. Natural clinical distemper has not been reported in this species [38], but vaccination-induced distemper may occur [39]. Similarly, there are no reports about cases of naturally occurring distemper in bush dogs (*Speothos yenaticus*), however, a possible vaccine-induced case has been described [40].

Endangered African wild dogs (*Lycaon pictus*) have been reported to be exposed to CDV and are highly susceptible to develop distemper [41,42]. Molecular analyses of isolates from African wild dogs suggest that CDV is endemic in wildlife carnivore populations in Tanzania (Serengeti ecosystem) [43,44]. Lethal lesions include interstitial pneumonia and suppurative to necrotizing bronchopneumonia with viral inclusion bodies and syncytial cells [43,44]. Besides natural infection, African wild dogs in captivity may also succumb to vaccine-induced canine distemper [45].

All genera of the tribus true foxes, i.e. *Vulpes* sp., including *Vulpes lagopus* (syn. *Alopex lagopus*), *Urocyon* and *Otocyon*, are susceptible to CDV infections and may develop clinical disease. CDV infections have been reported in red foxes (*Vulpes vulpes*) from various European countries including Germany [46,47], Italy [48,49], Spain [50], and Portugal [51]. Disease has been reported also in swift foxes (*Vulpes velox*) [52], kit foxes (*Vulpes macrotis*) [52], Indian foxes (*Vulpes bengalensis*) [53], and fennec foxes (*Vulpes zerda*) [54]. Infected foxes show abnormal behavior including loss of fear for humans, disorientation, and/or respiratory distress. Morphologic findings comprise mainly conjunctivitis, pustular dermatitis, lymphohistiocytic polioencephalitis, and bronchointerstitial pneumonia with viral inclusion bodies and syncytia [14].

Recently, the emergence and spread of a single genetic cluster within the Europe-1 clade of CDV among foxes and other wild carnivores in the Alpine region has been reported indicating the ability of this virus to replicate in a wider host range [55]. In gray foxes (*Urocyon* sp.), CDV outbreaks might have caused a dramatic population decline of Santa Catalina Island foxes (*Urocyon littoralis catalinae*). Sequence analyses indicate virus transmission from infected mainland USA raccoons unintendedly introduced to the island [56]. Mainland gray foxes (*Urocyon cinereoargenteus*) are susceptible to natural distemper and vaccine-induced distemper [57]. Crab-eating foxes (*Cerdocyon thous*) show neurological signs and succumb to CDV infection [58]. Free-ranging culpeo (*Dusicyon culpaeus*) and South American gray foxes (*Dusicyon griseus*) have been exposed to CDV [59]. Similarly, in the Serengeti-Mara ecosystem of East Africa, bat-eared foxes (*Otocyon*