



## Short Communication

# Neuropathology of natural canid alphaherpesvirus 1 infection in dogs

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Submitted: November 8<sup>th</sup>, 2022. Accepted: March 25<sup>th</sup>, 2023.

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**Abstract**

The neuropathology of canid alphaherpesvirus 1 (CaHV-1) infection in dogs has been reported, but the importance of the cerebellar lesions in the routine diagnosis remains relatively understated in the veterinary literature. Here we characterize the neuropathology of natural CaHV-1 infection in 25 dogs. The disease affected predominantly male dogs (22 cases). Clinical signs in 15 cases varied and sudden death was reported in 10 cases. All dogs had the typical areas of necrosis and hemorrhage in multiple organs with eosinophilic intranuclear viral inclusions in epithelial and/or inflammatory cells in multiple organs in 21 cases. Cerebral swelling and reddening were reported in 3 cases. Neurohistologic changes consisted of mild lymphoplasmacytic meningoencephalitis with occasional vasculitis and widespread glial nodules. Rare intranuclear viral inclusions (4 cases) were observed in endothelial cells or inflammatory cells in glial nodules. Cerebellum was examined in 11 cases and had extensive segmental necrosis of Purkinje cell layer (8 cases) and granule neurons in the internal (9 cases) or external (2 cases) granular cell layer. Intranuclear viral inclusions were observed in 8 cases and occurred in necrotic granule neurons in the inner granular cell layer (7 cases), outer granular cell layer (2 cases), Purkinje neurons (1 case), or endothelial cells (1 case). Diagnostic confirmation in 23 cases was based on routine histology and fluorescent antibody testing for CaHV-1 on fresh or frozen tissue samples. A routine diagnosis was based solely on the visualization of intranuclear viral inclusions in 2 cases.

**Keywords:** neuropathology, cerebellum, canid alphaherpesvirus 1, CaHV-1, dogs.

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Canid alphaherpesvirus 1 (CaHV-1) is a DNA virus with worldwide distribution that causes fatal multisystemic necrotizing and hemorrhagic disease in young puppies and subclinical to mild respiratory, reproductive, and ocular disease in adult and typically immunosuppressed dogs (2, 7). The low body temperature of newborn puppies plays a major role in their susceptibility to systemic CaHV-1 infection (2). Infection in puppies is mainly transplacental but can also occur during birth, after contact with secretions from infected littermates or the dam, or indirectly from fomites or the environment (2). Primary viral replication takes place in epithelial cells at the site of infection, with subsequent hematogenous dissemination and systemic disease (2). Individuals that survive acute disease undergo latent viral infection

in the tonsils, lymph nodes, respiratory tract, reproductive tract, and trigeminal ganglia (1, 7, 8). Latently infected dogs become a source of CaHV-1 to other susceptible dogs following viral reactivation during immunosuppression (2). Clinical disease is typically fulminant and affects puppies with less than 4 weeks of age. Although most infected patients die suddenly, others can develop lethargy, anorexia, abdominal discomfort, diarrhea, mucosal petechial hemorrhages, depression, opisthotonos, and seizures (2, 5, 7). Gross lesions are characterized by multiorgan necrosis and hemorrhage in the kidneys, liver, spleen, lungs, and intestines (5). Histologically, lesions consist of areas of coagulative necrosis and hemorrhage with scattered neutrophils and macrophages. Intranuclear eosinophilic viral inclusions in epithelial cells,

endothelial cells, and macrophages are highly suggestive of CaHV-1 infection and typically suffice for a routine diagnosis, but diagnostic confirmation is dependent on ancillary tests such as fluorescent antibody testing (FAT) and PCR (2, 5, 7).

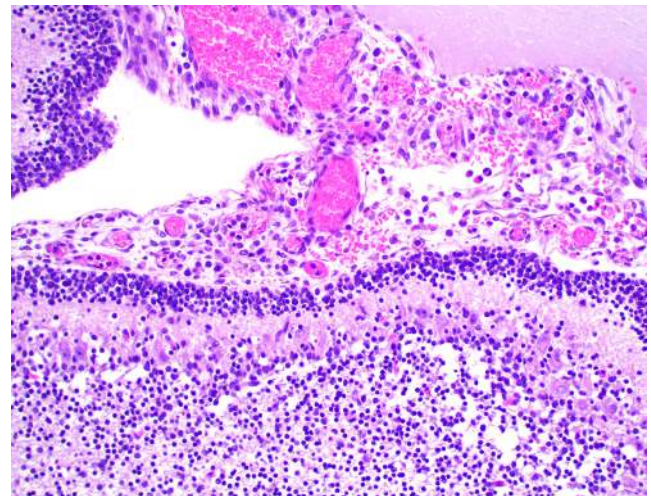
The neuropathology of CaHV-1 infection has been previously reported in natural and experimental cases (6, 9, 11). The current study briefly characterizes the neuropathology of natural CaHV-1 infection in 25 dogs, confirming the importance of the severe cerebellar lesions for a routine diagnosis of CaHV-1 infection in the brain.

A retrospective search of the Athens Veterinary Diagnostic Laboratory Web-based archives was performed for autopsy cases of CaHV-1 infection with central nervous system (CNS) involvement in dogs diagnosed from 2012 to 2022 using the search terms canid alphaherpesvirus 1, canine herpesvirus 1, CaHV-1, and CHV-1. Submission forms and autopsy reports from retrieved cases were reviewed and cases were included in the current study if CNS lesions were reported and CaHV-1 infection was confirmed by the presence of viral inclusions on routine histology or by ancillary testing using fresh or frozen tissue samples. Archived hematoxylin and eosin-stained slides were reviewed and neuropathologic changes were assessed according to the methods used in a previous study to characterize the neuropathologic changes affecting the telencephalon, cerebellum, and brainstem (12).

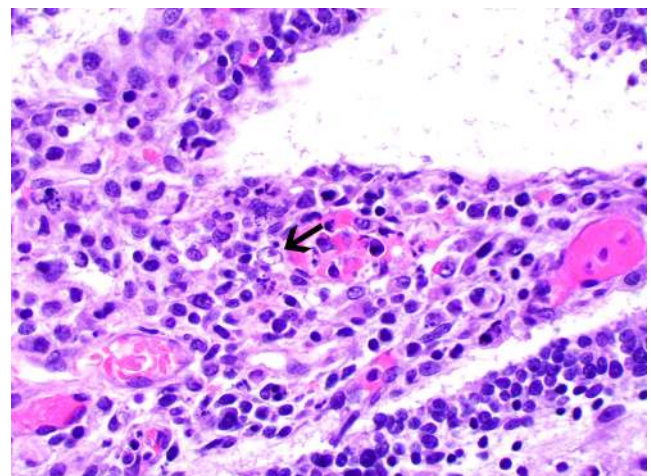
A total of 25 confirmed cases of CaHV-1 infection with CNS involvement met the selection criteria and were included in the current study. The disease affected 22 male and 3 female dogs with ages varying from zero days (newborn) to 30 days (median age = 10.7 days). Affected breeds included mixed breed (7 cases), Cavalier King Charles Spaniel (6 cases), English Bulldog (5 cases), Doberman Pinscher (2 cases), Labrador Retriever (2 cases), French Bulldog, Golden Retriever, and Perro de Presa Canario (1 case each). Clinical signs were reported in 15 cases and consisted of dyspnea (7 cases), anorexia (6 cases), vocalization (6 cases), nasal discharge (2 cases), weakness, nystagmus, and depression (1 case each). Sudden death was reported in 10 cases. Affected dogs died in 22 cases and were euthanized in 3 cases. Gross lesions consisted of distinct bright red hemorrhagic foci in the kidney (25 cases), liver (19 cases), intestinal serosa (9 cases), lung (8 cases), and spleen (7 cases). Histologically, all dogs had multiorgan necrosis and hemorrhage in the kidneys (25 cases), liver (23 cases), lungs (19 cases), spleen (16 cases), intestine (10 cases), myocardium (9 cases), and adrenal glands (8 cases). Eosinophilic intranuclear viral inclusions occurred in 21 cases and occurred in epithelial and/or inflammatory cells in the kidneys (18 cases), liver (13 cases), lungs (6 cases), adrenal glands (4 cases), spleen (2 cases), and intestine (1 case).

In the brain, gross lesions were reported in 3 cases (case 9, 10, and 16) and consisted of cerebral swelling with leptomeningeal reddening. Histologically, inflammatory changes occurred throughout the brain, with necrotic changes

occurring predominantly in the cerebellum. Lesions consisted of collections of a small number of lymphocytes surrounding leptomeningeal vessels in the telencephalon and cerebellum in all cases (Fig. 1). Leptomeningeal vasculitis (13 cases) (Fig. 2) was characterized by infiltration and effacement of vascular walls by lymphocytes and nuclear debris in the telencephalon (8 cases) and cerebellum (7 cases). Lymphocytic perivascular inflammation also occurred in the telencephalic gray (2 cases) and white matter (8 cases). Glial nodules (Fig. 3) occurred throughout the telencephalon (gray matter in 13 cases and white matter in 5 cases), cerebellum (gray matter in 6 cases and white matter in 9 cases), and brainstem (11 cases). Rare intranuclear viral inclusions were observed in endothelial cells in the leptomeninges and small



**Figure 1.** Canid alphaherpesvirus 1 infection, brain, dog (case 11). A small number of lymphocytes are distributed throughout the cerebellar leptomeninges (H&E).



**Figure 2.** Canid alphaherpesvirus 1 infection, brain, dog (case 11). Lymphocytes and cell debris efface the wall of a cerebellar leptomeningeal vessel. An intranuclear viral inclusion (arrow) is present in an endothelial cell (H&E).

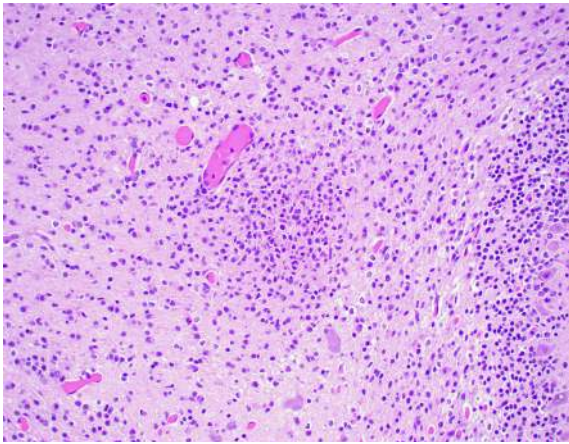
neuroparenchymal capillaries (3 cases) or within glial nodules (1 case).

Cerebellum was available for examination in 11 cases and had pronounced lesions with an increased number of intranuclear viral inclusions when compared to the telencephalon and brainstem. Cerebellar lesions (Figs. 4-6) consisted of variable degrees of segmental necrosis of Purkinje cell layer (8 cases) and granule neurons in the internal (9 cases) or external (2 cases) granular cell layer. Intranuclear viral inclusions were observed in 8 cases and occurred in necrotic granule neurons in the inner granular cell layer (7 cases), outer granular cell layer (2 cases), Purkinje neurons (1 case), or endothelial cells (1 case).

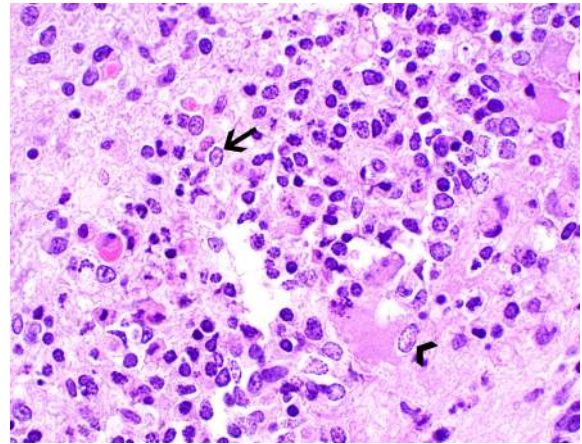
Diagnostic confirmation in 23 cases was based on routine histology and FAT for CaHV-1 on fresh or frozen samples of kidney (17 cases), lung (3 cases), liver (1 case), or a combination of kidney, lung, and liver (2 cases). A routine

diagnosis was based solely on the visualization of intranuclear viral inclusions in 2 cases.

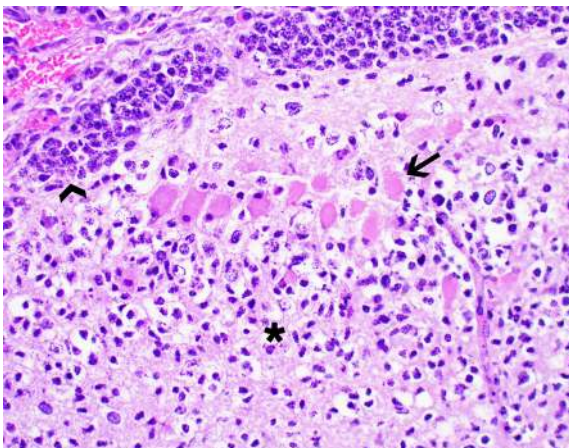
The neuropathologic changes associated with CaHV-1 in the current 25 cases are similar to those previously described in affected dogs (6, 10, 11). Although the visceral gross lesions caused by CaHV-1 infection are widely described and easily recognized during autopsy, the gross neuropathologic changes of CaHV-1 are poorly characterized (6, 9, 11). Reported gross lesions in the brain of 3 cases in the current study consisted of cerebral swelling and leptomeningeal reddening, likely resulting from edema and hemorrhage caused by the vascular changes. However, a detailed assessment of these gross lesions could not be conducted due to the retrospective nature of this investigation. Histologic lesions in the brain consist of mild lymphoplasmacytic leptomeningitis with vasculitis, widespread glial nodules, and cerebellar cortical necrosis (6). Although the characterization of the



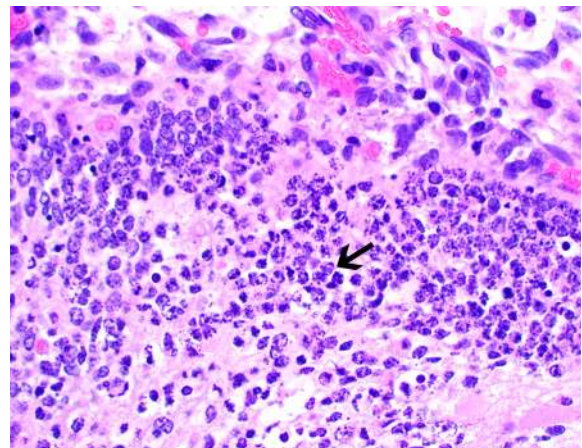
**Figure 3.** Canid alphaherpesvirus 1 infection, brain, dog (case 17). A glial nodule (center) partially effaces the cerebellar white matter (H&E).



**Figure 5.** Canid alphaherpesvirus 1 infection, brain, dog (case 18). Intranuclear viral inclusions in necrotic Purkinje neurons (arrowhead) and inner granule neurons (arrow) (H&E).



**Figure 4.** Canid alphaherpesvirus 1 infection, brain, dog (case 11). Extensive necrosis of Purkinje neurons (arrow) and inner granule neurons (asterisk) with scattered necrosis of outer granule neurons (arrowhead) (H&E).



**Figure 6.** Canid alphaherpesvirus 1 infection, brain, dog (case 22). Intranuclear viral inclusions (arrow) in outer granule neurons (H&E).

inflammatory infiltrates was not in the scope of this manuscript, inflammatory cells reportedly consist of T lymphocytes and fewer B lymphocytes, and the glial nodules have strong immunolabeling for Iba1, supporting their macrophagic/microglial origin (6).

Cerebellum was examined in less than 50% of the cases in this study. The reason for the low number of cases in which cerebellum was evaluated could be the lack of standardized CNS tissue collection and sampling during autopsy, the large number of personnel involved in tissue collection during autopsy, or to the fact that the diagnosis was likely suspected or known before histologic evaluation was conducted, allowing the pathologist to select a lesser number of tissues to be examined (3). The presence of distinct cerebellar changes is not surprising given the predilection for CaHV-1 replication in the developing cerebellar granule neurons of susceptible puppies (6). Although the typical signalment of affected dogs and the systemic pathologic changes caused by CaHV-1 infection suffices for a presumptive diagnosis of CaHV-1 infection, the absence or low number of viral inclusions in a number of cases may require additional testing such as FAT and PCR for diagnostic confirmation (1). The evaluation of cerebellum in our study revealed intranuclear viral inclusions in necrotic neurons in 72% of cases compared to 16% of the cases in the other parts of the brain. The striking differences in degree and nature of the cerebellar changes when compared to the brainstem and telencephalon in our study and in other investigations supports the routine inclusion of cerebellum during histologic examination in cases of CaHV-1 infection, especially if evaluating only CNS tissues (6).

### Conflict of Interest

The authors declare no competing interests.

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