# Rosie's Neurologic Conundrum

A Case Report of Progressive Canine Distemper Virus

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## Introduction

Canine distemper virus (CDV), currently known as Canine morbillivirus, belongs to the Paramyxoviridae family, genus Morbillivirus, and is the etiological agent of canine distemper.[1] CDV is an enveloped RNA virus. Its enveloped portion (the fragile lipid bilayer surrounding the viral particle) allows it to easily be killed with disinfectants because of an available attachment protein. Any disinfectant with detergent activity effectively inactivates this virus.[2] However, being an RNA virus allows for a higher mutation rate as compared to nonenveloped (but sturdier) DNA viruses. Antigenic drift and strain diversity have been increasingly associated with outbreaks, allowing for new strains to emerge; Therefore, monitoring is important to ensure current vaccines are fully protective against predominant circulating strains.[2] While domestic dogs are considered the reservoir species, CDV affects wildlife species (raccoons, skunks, foxes, ferrets) and can infect large felids (lions).[2]

CDV was first discovered in 1760 and is considered a highly contagious and acutely febrile disease in dogs.[3] It is associated with multiple cell tropism (epithelial, lymphoid and neurological), which leads to a systemic infection including respiratory, digestive, urinary, lymphatic, cutaneous, skeletal, and central nervous system (CNS) diseases.[4] CDV is found worldwide and commonly occurs in areas with low vaccine use.

## History and Presentation

Rosie, a 9-week-old female German Shepherd, presented to Mississippi State University College of Veterinary Medicine Internal Medicine Department on July 10, 2019 with a 1.5-week history of vomiting, diarrhea, and lethargy that progressed to possible seizures. Prior to illness,

she was an indoor-outdoor dog with one adult German Shepherd housemate who was up to date on vaccinations. There had been no known dietary indiscretion or exposure to toxic substances.

Prior to presentation at MSU, Rosie was managed by the referring veterinarian and emergency veterinarian in the Memphis area and was maintained on IV fluids, levetiracetam, and rescue doses of diazepam. She was parvo tested twice, both of which were negative. Rosie developed small red bumps covering her abdomen 2 days before arriving to MSU. Dermatologic findings of CDV can include pustular dermatitis in puppies.[8] Rosie had seizures overnight at the emergency clinic and was referred to MSU-CVM. Rosie was acquired from a breeder approximately 3 weeks prior to presentation. She received a modified live DA2PP vaccine on 6/24/19 and has no other vaccine history. If Rosie's birth date (5/19/19) was accurate, she received this vaccine at 37 days old (5 weeks and 2 days). According to the American Animal Hospital Association's (AAHA) 2017 canine vaccination guidelines, the distemper vaccine should be administered as early as 6 weeks of age and sequential doses administered at an interval of 2 to 4 weeks until at least 16 weeks of age.[12] Modified live vaccines are developed to induce an immune-response (humoral and cell-mediated) that mimics natural infection but without the disease-producing ability.[12] Modified live vaccines are highly immunogenic and are capable of inducing a sustained, protective immune response with one dose (in the absence of maternally derived antibody (MDA)).[12] However, the presence of MDA complicates the issue and is considered the primary cause of vaccine failure in young dogs.[13] To overcome interference by MDA, and ensure protection when maternal antibody levels wane, it is recommended to vaccinate puppies repeatedly between 6 and 16 weeks of age.[14] The maternal antibodies to distemper in puppies decline to levels deemed insignificant by 10-12 weeks of age.[13] One study compared the antibody titers of 6 week old puppies who were vaccinated and were MDA-

positive to puppies who were vaccinated and were MDA-negative. They showed that the antibody titers for CDV in the vaccinated MDA-positive puppies were at or below the limit of quantification (<1:2) prior to the second vaccination having shown a rapid decline over the proceeding weeks.[14] In the three weeks after second vaccination titers increased to similar levels as found two to three weeks after the first vaccination in MDA-negative dogs.[14] The presence of maternal antibody clearly limits the initial impact of vaccination on young animals, but subsequent boosting with a second vaccination even in the presence of some residual maternal antibodies increases the responses to the distemper vaccine antigens.[14]

When Rosie presented to MSU-CVM Internal Medicine Department, a complete physical exam was performed. Upon presentation, Rosie was quiet and alert but had a decreased response to stimuli. Her temperature, pulse, and respiration were all within normal limits. She had a body condition score of 2/9 and was approximately 5% dehydrated. Rosie was small and unthrifty in appearance. Subtle rhythmic twitching was appreciated over the muzzle and ears. Myoclonus (an irregular involuntary contraction of a muscle or group of muscles) is one of the more common signs seen with CDV infection and can manifest as a chewing motion of the jaw.[2] Rosie stood with a hunched posture, but her abdomen was soft and non-painful on palpation. Physical exam was otherwise unremarkable.

**Pathophysiology**

CDV is considered a multi-cell pathogen that has the ability to infect three different types of host cells including epithelial, lymphoid, and neurological cells.[5] While viral particles can be contracted from nearly all bodily fluids or inanimate objects, CDV is most commonly transmitted through inhalation of aerosolized viral material. Within a day of viral contact of the respiratory epithelium, the virus replicates in dendritic cells and macrophages and these infected

cells are carried to nearby lymph nodes. T and B-cells become infected and allow for viral expansion resulting in primary viremia. The virus spreads to secondary lymphoid tissues and ultimately results in total immune system compromise. CDV then spreads hematogenously to epithelial cells of the respiratory, gastrointestinal (GI), and urogenital tracts, as well as the central nervous system (CNS).[6] Dissemination of the virus to distal sites including liver, skin, GI tract, genitals, and respiratory mucosal surfaces results in the virus' spreading and subsequent transmission to uninfected individuals.[7] Epithelial and CNS tissues are typically affected by day 8 to 9 post-infection.[6]

If an animal can mount an effective cell-mediated and humoral immune response by day 14, no signs of clinical illness may be noted and the virus can be cleared from tissues.[8] Dogs that fail to mount an immune response by days 9-14 typically experience severe clinical signs and can die acutely.[9]

There are numerous ways CDV invades the CNS. One of the most crucial routes of neuro-invasion extend via infected peripheral blood mononuclear cells (PBMCs) that are transported through the blood brain barrier; afterwards, there is a virus release that results in the infection of resident epithelial and endothelial cells.[4] Viral persistence and neurological disease is related to the CDV viral cell-to-cell spread within astrocytes, allowing the virus to avoid the immune system detection.[5] Encephalitis can occur quickly if animals are young and/or are immunocompromised. Neuronal death is the direct result of viral-mediated destruction and indirectly by inflammation caused by CD8+ cytotoxic T cells which further stimulates reactive inflammatory cells. Chronic cases of encephalitis occur when CDV antibodies react with infected immune cells causing a release of oxygen radicals, resulting in demyelination of axons.

**Diagnostic Approach/Considerations**

Upon Rosie's arrival at MSU, a complete blood count, serum chemistry and a blood smear were submitted for analysis. The complete blood count revealed a mild anemia, mild hemoglobinemia and a mild neutrophilia. The chemistry panel revealed a mild hypocapnia, mild decrease in creatinine, mild hypoproteinemia, mild hyperphosphatemia and mild to moderate elevation in creatinine kinase. The blood smear examined did not detect any distemper inclusions. A sample of Rosie's conjunctiva was smeared on 2 glass slides and submitted to the Mississippi Veterinary Research and Diagnostic Laboratory for a canine distemper virus fluorescent antibody test which revealed a negative result. Additionally, blood was submitted for canine distemper antibody titers which revealed an IgM < 1:2 (negative) and IgG 1:32 (positive), indicating either exposure to a distemper vaccine or actual distemper infection. A single titer result does not differentiate between vaccine status and exposure.[11] Therefore, when being used as a tool to diagnose clinical disease, it is imperative to send paired samples (acute and convalescent) drawn approximately 2 weeks apart to monitor any significant changes in antibody titers.[11] Generally, a 4 fold increase in titers between paired samples is a good indication of recent infection.[11] Lastly, thoracic radiographs were obtained and revealed a normal cardiac silhouette, small pulmonary lobar arteries and veins and normal pulmonary parenchyma. There were several smoothly marginated, tubular, approximately 22 x 4 mm mineral opaque structures within the stomach. There was a decreased abdominal serosal detail. Interpretation of these thoracic radiographs are as follows: 1) decreased size of the pulmonary vasculature, possibly due to hypovolemia, anemia, or dehydration; 2) Gastric foreign material was evident. 3) Decreased abdominal serosal detail (poor contrast between abdominal organs), likely a normal variant for the age of the patient, since puppies and kittens do not have adequate fat accumulations within their abdomen.

On 7/17/19 blood was submitted for another set of canine distemper antibody titers and on 7/19/19, Rosie's second set of distemper titers revealed an IgM < 1:2 (negative) and IgG 1:512 (positive), confirming the suspected distemper infection.

**Treatment and Management *Including client communication***

Over the 7 days prior to her death, Rosie was medically managed in isolation wards 7/10/19, placed on seizure watch and monitored on camera. She received intravenous (IV) Normosol R at a fluid rate of 20 ml every hour, levetiracetam 30 mg/kg (1ml) IV every 8 hours, ampicillin/sulbactam 30 mg/kg (3.3ml) IV every 8 hours and midazolam 0.5 mg/kg (0.33ml) IV as a rescue dose for seizures.

Specific treatment for CDV does not currently exist and management is provided via supportive care. Treatment with fluids, whether IV or subcutaneous (SQ) is often necessary to reverse dehydration and replace ongoing fluid loss. Coupage and nebulization may be beneficial in cases of bronchopneumonia.[10] With pneumonia caused by CDV, secondary bacterial infections can be common, supporting the use of broad-spectrum antibiotics. For cases with seizures, anticonvulsant therapy is required.

Rosie ate and drank well the next morning after admissions to MSU (7/11/19) and appeared more alert than on arrival, although she still exhibited diarrhetic stools. She attempted to bite her handlers during treatment. Owners were informed that prognosis for return to function was low considering suspicion of distemper, and thus were informed that if they wanted to make a quality of life decision based on prognosis, that it was an option. Owners decided to continue therapy. Owners were informed that if Rosie passed (due to disease or if they elected euthanasia) that her remains would need to be sent in for testing for potential zoonotic disease. The next

morning (7/12/19), Rosie was laterally recumbent, listless and vocalizing. She was shaking and trembling and did not eat well. Owners were informed that Rosie was not doing well and not very responsive, but owners wanted to wait on distemper titers before a quality of life decision was made. Rosie had a seizure later that morning and a rescue dose of midazolam was given. Owners were informed of Rosie's seizure-like episode and that the medication given caused sedation but did not resolve her twitching. We advised the owners that in cases with distemper, very few dogs make it to adulthood and those that do have long term consequences secondary to the disease. In addition to her other medications, Rosie was started on metronidazole 10 mg/kg (6.6ml) IV every 12 hours, sucralfate 1 gram, 0.5 tablet dissolved in water, by mouth, every 8 hours and pantoprazole 1 mg/kg (0.82ml) IV every 12 hours. Owners elected to change Rosie's code status to do not resuscitate. The following morning (7/13/19), Rosie was still laterally recumbent, listless and vocalizing. She was shaking and had facial twitching. She became alert when offered food, ate well and drank water. She was still having diarrhea but had 1 normal stool. The following morning (7/14/19) Rosie was walking around in her cage, head pressing, circling to the right and vocalizing. She was still shaking but seemed to have less facial twitching, subjectively. She ate all food offered and drank water. She continued to have normal urination. The owners were informed that distemper titers were still pending, but to recognize that if Rosie received a distemper vaccination, the test would only show she's been exposed to the disease (either vaccine or actual infection). Later that day, Rosie's distemper titer results revealed an IgM < 1:2 (negative) and IgG 1:32 (positive). The next morning (7/15/19) Rosie was laterally recumbent, whimpering, face twitching and very unbalanced. She was neurologically inappropriate and while eating, began chewing her front paw and whining out from pain. She was unable to balance while eating but ate well. She continued to have diarrhea. Owners visited

with her today and were informed of Rosie's ongoing neurological deficits and decreased quality of life. Owners were warned that distemper can be shed for 3-4 months after exposure, so Rosie should not be around other dogs, especially puppies. Owners were sent home with a quality of life scale. All IV medications and fluids were discontinued due to continual compromise of her IV catheter. Her treatment now consisted of Normosol R 150 mls subcutaneously every 8 hours, levetiracetam 30 mg/kg (1.2ml) by mouth every 8 hours, midazolam 0.5 mg/kg (0.33ml) IV as a rescue dose for seizures and amoxicillin/clavulanic acid 11 mg/kg (0.7mls) by mouth every 12 hours. The following morning (7/16/19) Rosie appeared to be about the same: laterally recumbent, whimpering, face twitching, very unbalanced and neurologically inappropriate while eating. She was unable to stand without assistance. She continued to eat well, but her ability to prehend food seemed decreased. She was having formed stools as compared to diarrhea. On the morning of 7/17/19 Rosie was laterally recumbent and unable to balance herself without assistance. She ate half of the offered food and drank little water. Her ability to prehense food had decreased. It appeared as though she was becoming increasingly agitated and uncomfortable. Owners were informed of her status and they seemed interested in researching some ideas for supporting her neurologic conditions at home. That night, it was noticed that Rosie had self-traumatized her front paw pads by persistently circling in lateral recumbency and her owners were informed of this change.

**Case Outcome**

On the morning of 7/18/19 Rosie was laterally recumbent and unable to right herself. She was neurologically inappropriate and did not want to eat much but drank a little water with a syringe. Her owners were informed that Rosie appears to be suffering and her condition was

worse. Rosie's owner was able to visit with her and elected for humane euthanasia. Rosie's body was sent for a necropsy and cremation.

No gross lesions were observed on necropsy. Histopathology revealed the following: The brainstem had focally severe perivascular lymphoplasmacytic encephalitis with gliosis, neuronal necrosis, edema, intralesional spheroids, and numerous intranuclear and intracytoplasmic viral inclusions. The cerebral cortex and cerebellum contained multifocal moderate perivascular lymphoplasmacytic encephalitis with gliosis, neuronal necrosis, edema, intralesional spheroids, occasional intranuclear and intracytoplasmic viral inclusions, and multifocal marked white matter demyelination. The histopathology described above, in addition to Rosie's clinical signs, are consistent with the diagnosis of CDV infection.

Rosie's brain was submitted to the Mississippi Public Health Laboratory for rabies testing via direct fluorescent antibody detection. Results: no particles characteristic of rabies infection were seen.

Tissues from Rosie's brain, lungs and bladder, in addition to urine, were submitted for canine distemper polymerase chain reaction (PCR) and were positive.

Canine distemper PCR sequencing was sent off for identification. The partial sequencing analysis of nucleocapsid protein (N) gene indicated that Rosie's distemper isolate shared a 99% match with the published isolates CDV UEL/PR-SAH2. While there is only one serotype of CDV, there are considerable differences in the pathogenicity and therefore of the gene sequence of different virus strains, mostly those of the central nervous system (CNS).[15] Some of these strains can cause disease in the gray matter of the CNS, which causes neuronal destruction early

on. Other strains are responsible for infecting the myelin (white matter) of the CNS and these will cause a delayed destruction.

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