Aleutian Mink Disease Parvovirus: Implications for Companion Ferrets

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ABSTRACT: Aleutian mink disease parvovirus (ADV) causes disease in mink and ferrets and can infect such related animals as raccoons, weasels, fishers, martens, and striped skunks. Severe Aleutian disease (AD) in adult mink is characterized by viral persistence, high levels of antiviral antibody (which is ineffective at eliminating the virus), and immune-complex disease. Death results when virus–antibody immune complexes deposit in the kidneys, producing immune-mediated glomerulonephritis. Ferrets infected with ADV are usually asymptomatic and maintain a low antibody titer, but severe disease can occur. Ferrets with clinical signs of AD may have chronic wasting disease (similar to that seen in mink) or neurologic disease (most often manifested as posterior paresis or paralysis).

A leutian mink disease parvovirus (ADV) can infect ferrets and is capable of negatively impacting the companion ferret population. Several reports of Aleutian disease (AD) in companion ferrets have been published during the past decade. In recent years, outbreaks have occurred in a ferret shelter and multiple-ferret homes. Despite the perceived increase in disease incidence in ferrets, little is known about incubation, transmission, interpretation of diagnostic tests, pathogenesis, treatment, and prevention of AD in ferrets. This article summarizes information about AD in mink and ferrets and provides suggested management options for affected companion ferrets.

HISTORY OF ALEUTIAN DISEASE IN MINK

Aleutian disease has long been considered primarily a disease of ranch mink

\(^\text{a}\)Greenacre C: Personal communication, University of Georgia, Athens, 2000.
Highly susceptible Aleutian mink (aa) carry two autosomal recessive genes for dilute coat color (producing a gun-metal gray peel) that is associated with Chédiak-Higashi syndrome, an inherited disorder of the immune system (Figure 1). ADV was named after Aleutian mink because of their unique susceptibility to AD. However, dark-coated mink that are heterozygous (Aa) or homozygous dominant (AA) are also susceptible to ADV infection but tend to have lower morbidity and mortality compared with Aleutian mink. AD was recognized as a disease syndrome in 1946 when mink ranchers realized the economic value of the gray pelts and began actively breeding Aleutian mink for their desirable coat color. The first published description of AD in mink appeared in 1956.

Before the identification of ADV, distemper and botulism were the primary disease concerns of mink ranchers. Ranchers commonly made their own autogenous distemper vaccines by homogenizing spleen from distemper-infected mink, making suspensions, and injecting all the mink on their ranch. This practice led to a severe outbreak of AD on a Connecticut ranch, with a mortality rate of almost 100% within 6 months. Over the ensuing decade, suspicions rose that AD was caused by a “filterable agent” (i.e., a virus). ADV was isolated and studied during the early 1970s but was not correctly characterized as a parvovirus until 1980. Extensive molecular characterizations of ADV and studies of its pathogenesis in mink have been published over the past 20 years. Although very distantly related to parvoviruses that cause acute gastrointestinal disease (e.g., canine parvovirus, feline parvovirus, mink enteritis virus), ADV is antigenically distinct from these members of the feline subgroup of paroviruses.

**AERICAN MINK IN FERRETS**

Many ferrets (Mustela putorius furo) were probably naturally exposed to ADV on mink ranches because some farmers raised mink and ferrets on the same property. Ferrets were also experimentally infected with ADV during the 1960s. Researchers believed that AD could be developed as an animal model for human immune-mediated diseases but sought an animal that was easier to handle than the sometimes ferocious mink. Ferrets were infected with tissue homogenates from infected mink or were closely housed with infected mink and ferrets. Although the ferrets did not develop clinical illness, they did acquire periportal lymphocytic cellular infiltrates in their livers, thymic hypoplasia, hypergammaglobulinemia, splenomegaly, and mesenteric lymphadenopathy. Glomerulonephritis and arteritis, hallmarks of AD in highly susceptible Aleutian mink, occurred in naturally infected ferrets but not in ferrets experimentally infected with material from mink. Mink ADV appeared to persist in the ferrets for 136 to 180 days.

Limitations of these early studies included the inability to detect and differentiate viral strains and easily test for preexisting antibody in the acquired research animals. The overall conclusions of studies conducted before 1985 were that there were distinct mink and ferret strains of ADV; the disease progressed more slowly in ferrets than in mink, and the disease and microscopic tissue changes were less severe in ferrets than in mink.

**CLINICAL DISEASE**

Manifestations of clinical disease are likely determined by virus strain and host genotype and immune status. Thus a broad array of clinical signs—ranging from clinical normalcy to nonspecific signs (e.g., lethargy, anorexia) to specific problems (e.g., uremia; neurologic dysfunction; frank hemorrhage of the digestive tract, including the mucosa of the oral cavity and intestines)—can be seen.

**Mink**

Aleutian disease was first manifested as a chronic wasting disease of adult Aleutian mink. Weight loss, poor pelts, lethargy, anorexia, polydipsia, anemia, and melena were common clinical signs in affected mink. Infertility, small litters, and high stillborn rates were also noted. Necropsy examinations of end-stage infected animals classically showed small, shriveled kidneys; splenomegaly; mesenteric lymphadenopathy; hepatomegaly; and blood in the intestinal tract. Aleutian mink experimentally infected with virulent strains of...
ADV tested positive for anti-ADV antibodies (endpoint titers were 1024 or greater using counterimmunoelectrophoresis [CIEP]), tested persistently positive when polymerase chain reaction (PCR) was used to detect nucleic acid in the serum, were hypergammaglobulinemic (i.e., more than 20% of total serum proteins were γ-globulins), and were aseptic in end-stage disease.\textsuperscript{24,25} Virus was found in the cytoplasm of such phagocytic cells as macrophages and dendritic cells\textsuperscript{26,27} and in renal tubular epithelial cells.\textsuperscript{28}

Adult non-Aleutian mink may develop one of three general types of ADV infection: progressive AD as described for Aleutian mink;\textsuperscript{2} persistent nonprogressive infection; or nonpersistent, nonprogressive infection with eventual clearance of the virus.\textsuperscript{10} Whether these three categories apply to ferrets is unknown.

The target cells for viral replication are different in newborn kits compared with adult mink.\textsuperscript{17} In contrast to the protracted infection of macrophages and dendritic cells in adult mink, kits infected within the first 2 weeks of life developed rapid viral replication in the alveolar type II epithelial cells of the lungs.\textsuperscript{17,29,30} Direct viral damage rather than immune-mediated disease caused severe, fulminant, and often fatal pneumonia.\textsuperscript{17,29,30} The behavior of this acute infection of neonatal mink is more reminiscent of feline subgroup parvovirus infections (e.g., canine parvovirus, feline parvovirus, mink enteritis virus) than the persistent infection of adult mink with ADV.

**Ferrets**

Aleutian disease in ferrets was originally considered primarily a subclinical problem. One 1978 report and all studies of AD in ferrets published since 1990, however, have described overt clinical disease.\textsuperscript{1–3,31} Clinical syndromes included chronic wasting disease\textsuperscript{5,31} and neurologic disease consisting of posterior paresis or paralysis.\textsuperscript{21–3} Virus isolated from the spleen of an infected ed ferret (ADV-F\textsuperscript{3}) was amplified by PCR for DNA sequencing.\textsuperscript{32} The DNA sequence of a small segment of the capsid protein that makes up the virus “shell” showed that ADV-F was 88% to 89% identical to some previously sequenced pathogenic strains of mink ADV.\textsuperscript{32} DNA sequence differences confirmed that ADV-F was dissimilar to isolates identified in mink.\textsuperscript{32}

Clinical syndromes seen during a 1998 outbreak of AD in a ferret shelter in San Antonio, Texas, included generalized wasting and respiratory, neurologic, and cardiac forms of disease in ADV-positive ferrets.\textsuperscript{4} Ferrets with chronic wasting disease had small kidneys on necropsy and glomerulonephritis on microscopic examination. Respiratory disease in affected ferrets included severe coughing, right middle lung lobe consolidation and collapse, and serosanguineous pleural effusion. Microscopic examination of necropsy tissue samples revealed hemorrhagic interstitial pneumonia. Neurologic signs usually followed respiratory signs by several weeks but occurred alone in some ferrets. Neurologic dysfunction started as posterior paresis and either remained stable or progressed to ascending paralysis accompanied by urinary and fecal incontinence. A few ferrets developed heart disease reminiscent of ferret cardiomyopathy, but necropsy samples showed arteritis in the cardiac muscle (suspected to have resulted from immune-complex deposition) and lymphoplasmacytic infiltrates. Severe anterior uveitis also occurred in some ferrets. Uveitis has also been described in AD-affected mink.\textsuperscript{35}

All of these sick ferrets tested positive for anti-ADV antibody by CIEP, and viral DNA was amplified by PCR using tissue from some of these ferrets.\textsuperscript{34} DNA sequence analysis of these PCR products was identical to that previously reported for ADV-F.\textsuperscript{32,34} “To date, ADV-F is the only isolate of ADV in ferrets to be documented with published DNA sequence data.”\textsuperscript{32,34}

A multiple-ferret home in Dallas, Texas, experienced the loss of 2 of 11 ferrets in the spring of 2000.\textsuperscript{1} Both ferrets tested positive for antibody using CIEP and had microscopic tissue changes consistent with AD. One of these ferrets (a 5-year-old male) had an endpoint antibody titer of 256 by CIEP;\textsuperscript{35} hypergammaglobulinemia (32%), muscle twitches, and seizures; the liver and kidney showed extensive lymphoplasmacytic cellular infiltrates typical of AD. Glomerulonephritis was also identified in the kidney. Two of the remaining nine ferrets in this home also tested positive using CIEP; the other seven ferrets had not been tested when this article was written.

**DISEASE TRANSMISSION**

Natural horizontal transmission of ADV among mink is likely to occur by either the oral or aerosol route.\textsuperscript{36–38} AD has been experimentally transmitted between mink by inoculation with whole blood, serum, urine,\textsuperscript{25,37,39} feces, saliva, and bone marrow from infected mink.\textsuperscript{37}

Vertical transmission of ADV has also been shown to occur in mink.\textsuperscript{36,40} Dams with either progressive or nonprogressive subclinical infections were shown to have high numbers of infected kits.\textsuperscript{35} The risk for ADV infection in kits born to dams with nonprogressive subclinical infections was less than that for kits born to dams with progressive AD.\textsuperscript{36} Dams infected with ADV before mating had a higher percentage of dead and resorbed fetuses compared with dams infected after expected embryo implantation.\textsuperscript{40}

The natural route of transmission of AD among fer-
reets is unknown. Horizontal transmission is suspected, but whether infectious ADV is present in urine, feces, or saliva of infected ferrets is unknown. This information is critical to help companion ferret owners prevent transmission of the virus from infected to noninfected ferrets in their homes. It is likewise important for ferret clubs in terms of establishing rules regarding the admission of infected animals in ferret shows. Vertical transmission in ferrets has been suspected but not studied. Knowledge of the mechanisms of horizontal and vertical transmission is crucial for ferret breeders to be able to make decisions about acquiring new ferrets for breeding programs, monitoring breeding ferrets, and placing young jills and hobs in companion homes.

Disease transmission is an area that needs to be researched. Detection of infectious virus in blood or cell-free body fluids may help identify ferrets that are currently shedding the virus. This information would also be valuable in learning more about ADV transmission in ferrets.

**DIAGNOSTICS**

Counterimmunoelectrophoresis is the standard for detecting anti–ADV antibodies in mink and ferrets. This test is a precipitation reaction between antibody in serum samples and a commercial viral antigen (Table I). It detects antibodies directed against the capsid proteins comprising the protective “shell” around the viral genomic DNA. A simple positive or negative result is given. CIEP has primarily been used for test-and-slaughter programs on mink ranches, in which more detail about the expense of the test.

As mentioned, CIEP cannot distinguish among immunoglobulin subclasses. In ADV-infected mink, IgM increases as soon as 6 days after inoculation and peaks at 15 to 18 days after inoculation. IgG is not detected until at least 12 days after infection but is consistently increased by 30 days after infection. IgG levels remain increased long after IgM levels have returned to normal. The appearance of antibodies of different subclasses has not been studied in detail in ferrets. Needed improvements in antibody testing include reporting endpoint titers and distinguishing between IgM and IgG subclasses. New diagnostic tests should be developed to complement the CIEP by providing these additional data, thereby helping clinicians determine the stage and severity of infection.

Hypergammaglobulinemia (excessive antibody production without neutralization of the virus) is a hallmark of AD in mink and can develop in infected ferrets. Serum protein electrophoresis is used to compare γ-globulin levels with the rest of the serum proteins. Most commercial laboratories conduct this test and require serum. Care must be taken during sample collection because hemolysis can interfere with the

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**TABLE I**

<table>
<thead>
<tr>
<th>Company</th>
<th>Cost</th>
<th>Accepted Sample</th>
<th>Payment</th>
<th>Results</th>
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<tr>
<td>United Vaccines, Inc.</td>
<td>$15 first sample; $10 each additional sample</td>
<td>≥10 µL whole blood or serum, preferably in a capillary tube</td>
<td>Prepayment is required; send check or credit card information with sample</td>
<td>48-hr turnaround; results are reported as positive, negative, or no sample (if tube breaks)</td>
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<td>ATTN: Customer Service</td>
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<td>2826 Latham Dr.</td>
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<td>Madison, WI 53713</td>
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<td>Phone: 800-283-6465, 608-277-2030</td>
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*Express overnight shipping recommended.
The presence of hy-

Evidence of glomerulonephritis and arteritis γ Levels of virus replication were not affected by 

This lower dosage was not as ef-

25 200). IMMUNOSUPPRESSANTS 46,47 Although the use of
these drugs has not been reported in ADV-infected ferrets, it may be reasonable to consider using immuno-suppressive oral prednisone therapy to decrease immune-mediated consequences of AD in carefully selected companion ferrets. A prospective clinical trial should be done to determine whether this treatment would be helpful for ferrets with AD.

Treatment of AD in ferrets will continue to be limited to supportive care until more definitive therapy is determined. Intravenous or subcutaneous fluid therapy may be necessary to maintain hydration. Maintaining a positive nutritional plane via temporary syringe or tube feeding may be needed in sick ferrets. Studies have shown that ADV-infected mink have a decreased ability to mount a humoral immune response. Thus monitoring ADV-infected ferrets for opportunistic infections and treating with appropriate antibiotics are important.

**DISEASE PREVENTION**

No vaccine against AD in mink or ferrets is currently available. In fact, the presence of additional antibodies directed toward capsid proteins exacerbates the chronic immune-mediated form of AD in mink. Despite this negative data, anticapsid antibodies have been shown to blunt the acute form of AD seen in mink kits, and antibodies generated against one of the nonstructural proteins (NS1) partially protected mink from immune-mediated AD—but not infection—in a recent vaccine trial. Therefore, there is still hope that a vaccine against ADV can be developed. Vaccine strategies must avoid generating anticapsid antibodies in adult animals and thus must focus on alternative targets for stimulating protective immunity. The expansion of the field of vaccinology in the past 10 years has brought promising new technology that adds practicality to the hope of developing an effective vaccine against ADV in ferrets.

Until an effective vaccine becomes available, the best recommendations for preventing the spread of AD among ferrets are isolation of uninfected ferrets from ADV-infected ferrets and environmental cleaning. We believe that the CIEP assay is currently the best method to detect ferrets that may be carrying ADV. Ideally, infected and noninfected ferrets should not be housed on the same property, but this is often impossible in multiple-ferret homes. Recent experiments using mink feces contaminated with mink enteritis parvovirus and kept under outdoor conditions showed that the virus survived for 5 to 10 months. Complete drying was helpful in inactivating the virus, and thus mechanical cleaning was as strongly recommended as was disinfection for environmental control. In all likelihood, ADV can survive in the environment in a similar fashion. Therefore, food and water bowls, toys, cages, carriers, litter-boxes, bedding, and carpeting contaminated with virus particles—particularly when accompanied by such organic material as feces—may serve as prolonged sources of virus for uninfected ferrets.

Contaminated environmental conditions would especially exist at ferret shows if ADV-shedding ferrets are present. With the current lack of knowledge regarding the pathogenesis of AD in ferrets and the limitations in identifying virus-shedding ferrets, there is no way to guarantee the safety of all ferrets at ferret shows. Restricting entries to ferrets with negative CIEP tests 3 to 4 weeks before the show would be prudent. The best protection for valuable AD-free breeding stock and companion ferrets is to eliminate their exposure to other ferrets of questionable ADV status.

**ACKNOWLEDGMENTS**

The authors thank Jeff Mauldin, BA, University of Georgia, and Jim Wolfinbarger, National Institute of Allergy and Infectious Disease, National Institutes of Health, Rocky Mountain Laboratories, Hamilton, MT, for technical support. They also thank the ferret owners who graciously provided samples from their pets for research purposes.

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The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. *Choose only the one best answer to each of the following questions; then mark your answers on the test form inserted in Compendium.*

1. AD, an immune-mediated, chronic viral infection of mink, ferrets, and related animals, is caused by a
   a. coronavirus. c. retrovirus.
   b. picornavirus. d. parvovirus.

2. The CIEP assay detects
   a. antigen. c. antibodies.
   b. immune complexes. d. CD8+ lymphocytes.

3. The two most common clinical syndromes of AD in ferrets are
   a. cardiomyopathy and urinary tract infection.
   b. glomerulonephritis and posterior paresis.
   c. uveitis and adrenal gland disease.
   d. thyroid disease and glomerulonephritis.

4. Hypergammaglobulinemia is detected using
   a. serum electrophoresis.
   b. total serum protein determination.
   c. albumin:globulin ratio.
   d. Western blot analysis.

5. Which of the following statements regarding transmission of ADV among ferrets is true?
   a. ADV has been proven to be shed in the urine, feces, and saliva of ferrets.
   b. The mode of transmission of ADV among ferrets is unknown at this time.
   c. ADV is known to be spread in the air.
   d. Transmission from dam to kit is known to occur in ferrets.

6. Which of the following factors does not affect the manifestations of clinical AD?
   a. host genetics
   b. viral strain
   c. host immune status
   d. host temperature

7. Which of the following statements regarding ADV in mink is true?
   a. Kits infected with ADV develop severe gastritis and glomerulonephritis.
   b. Classic disease in adults includes chronic wasting, glomerulonephritis, high antibody titers, and hypergammaglobulinemia.
   c. Classic disease in adults includes acute, severe bloody diarrhea, similar to that seen with canine parvovirus.
   d. Kits develop chronic wasting, glomerulonephritis, high antibody titers, and hypergammaglobulinemia.

8. Which of the following statements regarding ADV in ferrets is true?
   a. Isolation of AD-free ferrets from ferrets with questionable antibody status is the best way to prevent transmission.
   b. Current tests can guarantee that a ferret is not shedding ADV.
   c. Because ADV-F likely dies very rapidly in the environment, cleaning and disinfection are not important.
   d. It is unlikely that ADV-F can survive in food and water bowls, cages, carriers, and carpets.

9. Treatment of ADV in ferrets
   a. involves potent antiviral agents.
   b. requires DNA viral sequencing.
   c. consists of supportive care and possibly immunosuppressant agents.
   d. is not necessary because a vaccine is available.

10. Most ferrets that become infected with ADV
    a. are asymptomatic but maintain low antibody titers.
    b. become acutely ill and die suddenly.
    c. are immunosuppressed and chronically affected with opportunistic infections.
    d. suddenly become aggressive.