Article #4

CE

Reproductive Effects of Canine Herpesvirus

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ABSTRACT:

Canine herpesvirus type 1 has widely different effects, depending on the signalment of the exposed animal. Infection in adults is often inapparent, and latency follows. However, self-limiting lesions can occur on the genitalia of sexually active animals. Reproductive failure manifests as early fetal loss, late-term abortion, stillbirth, or the birth of compromised neonates. Recrudescence of infection in clinically normal animals can occur during periods of physiologic stress. Early neonatal infections result in fulminant sepsis and death, with rare survivors suffering permanent neurologic and cardiac deficits.

Canine herpesvirus type 1 (CHV1) occurs in canine populations throughout the world. Serologic surveys indicate a high level of infection in the general canine populace estimated to be greater than 40% in two European studies.[1,2] In an unrelated US study investigating canine respiratory disease, 6% of dogs had significant CHV1 titers during clinical disease.[3] In addition to variations in experimental technique among studies, accurately assessing the true level of infection by serologic methods is unlikely because antibodies to CHV1 are thought to persist for no more than 60 days.[4]

Using polymerase chain reaction (PCR) in other species has allowed detection of an increased prevalence of latent herpesviruses.[5] PCR has also demonstrated that tissue distribution within the individual host is wider than previously believed.[6,7]

Transmission occurs by oronasal and sexual contact. Although it has been theorized that CHV1 infection has a higher prevalence in regularly socialized dogs, a recent survey did not demonstrate increased occurrence in the general populace.[2] However, increased prevalence of infection has been demonstrated in dogs with reproductive problems.[8] For dogs living in colonies, studies investigating the difference in prevalence of CHV1 relative to the general population have been contradictory.[2,9,10]

CHV1 infection manifests as distinct clinical syndromes in adults, pregnant females, and neonates. In adults, localized mucosal and genital lesions occur at the site of viral inoculation after initial exposure and during viral recrudescence. Reproductive failure associated with exposure of naive pregnant dogs has been documented and is manifest as early fetal loss, late-term abortion, stillbirth, or the birth of compromised neonates.[11–13] In postnatal infections in neonates up to 3 weeks of age, an acute, generalized, near uniformly fatal syndrome occurs. After 3 weeks of age, neonatal infection can result in respiratory disease of varying severity.[4]

DESCRIPTION

Herpesviruses are divided into three subfamilies (α-, β-, γ-herpesvirus) based on genomic organization.[14] Those of veterinary importance (including CHV1) are predominantly in the α-herpesvirus group because they are chiefly

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mucosal pathogens that establish latency within sensory ganglia.

CHV1 is a double-stranded DNA virus with an icosahedral capsid that is 100 to 150 nm in diameter. The host range of CHV1 has been shown to be restricted to domestic and wild Canidae.[6,15] Other members of the α-herpesvirus group include equine herpesvirus types 1 (EHV1) and 4 (EHV4), bovine herpesvirus type 1 (BHV1), suid herpesvirus type 1 (SHV1; pseudorabies), and feline herpesvirus type 1 (FHV1). CHV1 has been shown to share 51% genetic homology with FHV1.[16]

COMPARATIVE EFFECTS OF HERPESVIRUSES ON REPRODUCTION

Infection with herpesviruses may cause reproductive and neonatal disease in a wide range of species. The ability of α-herpesviruses to cause leukocyte-associated viremia appears important in the pathogenesis of abortion. Viremia associated with EHV4 or FHV1 is rare, and these viruses do not often cause abortion.

In contrast, EHV1, which establishes a leukocyte-associated viremia, is considered the most important viral cause of equine abortion.[17] Vasculitis, focal infarction, and thrombosis of the microcotyledons of the placenta can occur. Replication of EHV1 in the endothelial cells of the pregnant uterus is followed by transplacental spread to the fetus. Virus can be recovered from fetal lung, liver, thymus, and spleen. EHV1 antigen can also be found in the fetal placenta vasculature.[18]

BHV1 is an important cause of vesicular genital lesions and reproductive failure in cattle. Strains vary in their virulence and pathologic effects.[19] In addition to early embryonic loss, placental degeneration and fetal infection leading to abortion, endometritis, and oophoritis can result.

SHV1 (pseudorabies) is unusual among α-herpesviruses because it results in high mortality in a wide host range.[20] Fetal and placental lesions result in abortion; however, maternal pyrexia subsequent to infection can in itself result in expulsion of fetuses that test negative for herpesvirus. Depending on the interval between maternal infection and abortion, varying degrees of fetal autolysis are present.

FHV1 has been the subject of intense research efforts and therefore has been better characterized than CHV1. FHV1 has a host range restricted to Felidae. All isolates examined constitute one serotype; however, minor differences in pathogenicity are apparent.[21] Unlike other α-herpesviruses (including CHV1), FHV1 has neither a predilection for the reproductive tract nor direct cellular effects there. Reproductive failure with this agent likely results from severe systemic maternal illness.[22]

Fetal pathology is consistent between host species, with the liver, kidneys, spleen, and adrenal glands being common sites of cellular destruction subsequent to α-herpesvirus infection.

Asymptomatic infection with canine herpesvirus is widespread within the domesticated dog population. However, infection with the virus may have serious consequences on naive gravid females and neonates.

ASPECTS OF LATENCY

Herpesviruses have the ability to cause lifelong latent infections.[14] As with many other DNA viruses, herpesviruses maintain a "persistent life strategy."[23] Following an initial period of productive infection and antiviral response, the virus is not fully cleared from the host and maintains the ability for continuous or intermittent reproduction. Latency of α-herpesviruses typically occurs in the sensory ganglia; however, the viruses have also been detected in lymphocytes during latent infection.[24] Inside these latently infected cells, uncoated viral genome persists as circular double-stranded DNA within the nucleus.

In addition to intracellular residence of viral DNA, herpesviruses also express virokines, which are responsible for altering the host inflammatory response to the virus. Virokines act as both chemokines and chemokine antagonists, modulating the dynamics of inflammatory cells.

CHV1 is well adapted to its host, causing insignificant disease or lifelong inapparent infection in most exposed dogs.[13] CHV1 has been shown to persist in a variety of tissues in naturally infected dogs.[6] The age at which infection was acquired by these animals was not known; hence, age-related effects on tissue localization have not been determined. Viral DNA amplification by PCR has detected virus in the trigeminal ganglia, lumbosacral ganglia, tonsillar tissue, parotid salivary gland, and liver.

PATHOGENESIS OF CANINE HERPESVIRUS

Because of the intermittent nature of productive phases of infections and the relative fragility of herpesvirus outside the cell, opportunities for viral transmission are limited. Transmission usually involves transfer from parent to offspring, sexual contact, or direct oronasal contact between shedding and susceptible animals. Fomite spread is rare.

CHV1 is a cell-associated infection and is spread by cell fusion or transportation. After epithelial replication at the site of entry, leukocyte-associated viremia disseminates the virus to a wide range of neural and lymphoid tissue. Systemic infection of a pregnant bitch can lead to placentitis and transmission to the fetus.[25] During the acute phase of infection, all dogs shed the virus in the nasal mucosa regardless of the route of infection.[26] Viral shedding and genital and respiratory infections can occur concurrently with circulating antibodies. Venereal transmission from infected males to susceptible females is not thought to be a significant mode of viral spread; however, genital localization in females is an important means of transmission to puppies at birth.[27]

Puppies may be infected vertically in utero by vaginal secretions during delivery or by secretions from the recently infected dam. The lumbosacral ganglion is an important site of latency, and recrudescent virus is a significant means of viral spread to neonates, which are highly susceptible.[6] Horizontal spread occurs by contact with an animal currently shedding virus, such as an infected littermate or acutely infected adult. Mortality is high because of the ability of the virus to replicate rapidly within immunologically immature neonates. In addition, the inability of neonates to thermoregulate to adult levels further favors viral replication.

As with other α-herpesviruses, stress (i.e., social, physiologic, environmental) or administration of immunosuppressive doses of corticosteroids has reactivated viral shedding in previously infected dogs[28]; this has been most fully defined in cats.[29,30] Recovery of active virus from bitches naturally infected with CHV1 was documented in vaginal, oral, ocular, and nasal discharges.[31]

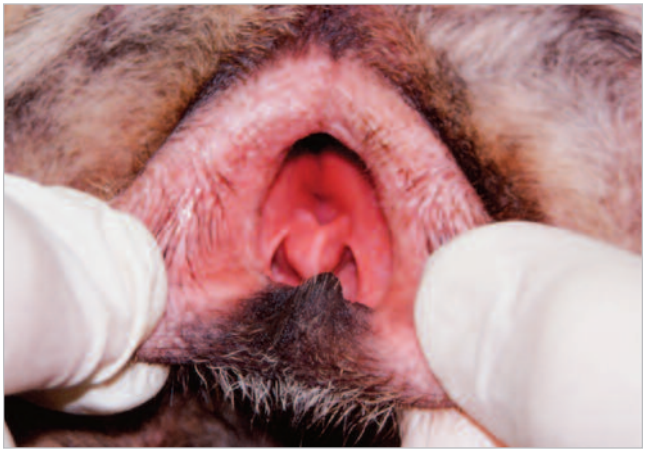

Figure 1. Genital lesions on a female dog. CHV1 may result in areas of vesiculation, hyperemia, and submucosal hemorrhage at the site of inoculation.

CLINICAL SYNDROMES

Manifestations of CHV1 infection depend on patient signalment.

Adult

Within the adult population, infection is widespread without overt clinical signs of disease. However, during the acute phase of the initial infection, lymphoid nodules, submucosal hemorrhage, and hyperemia (Figure 1) can occur at the site of mucosal viral inoculation.[11] Mild upper respiratory tract disease can occur in older puppies and adults.[32] Vesicular lesions have been noted to develop in females with the onset of proestrus and then spontaneously regress during subsequent anestrus.[27] Similar lesions can occur in males at the base of the penis and along the prepuce.

Pregnancy

Depending on the stage of gestation, inoculation of naive pregnant bitches with CHV1 can result in inapparent fetal loss, mummification, fetal death and expulsion, or premature delivery of live puppies. Previously exposed seropositive bitches usually produce normal litters. Maternal antibodies or immune lymphocytes acquired from the milk of seropositive bitches are capable of protecting puppies from the clinical consequences

of CHV1 infection.[27,33] Although the degree of this protection is variable, this is likely the mechanism whereby infected bitches produce clinically normal litters.

Neonate

The period of maximum susceptibility to CHV1-induced disease has been well characterized and is considered to be from 3 weeks before until 3 weeks after parturition.[4]

Prenatal exposure can cause disease ranging from fetal loss to delivery of apparently healthy puppies, depending on gestational age when infection occurs. Clinical presentation can vary within the same litter, and it is important to realize that not all puppies may be infected. Death of neonates due to CHV1 before 1 week of age likely indicates prenatal infection.

Postnatal exposure is more common. In litters exposed during delivery or subsequently, illness predominantly occurs at 1 to 3 weeks of age. The incubation period is 3 to 7 days after infection. Clinical signs lack specificity but include rapid shallow respiration, abdominal pain, refusal of food, and vomiting.[27] Following the onset of illness, death ensues within 2 days.

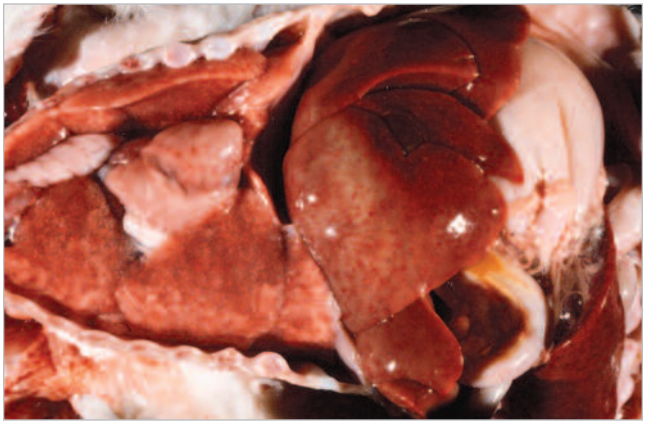

Figure 2. Neonatal death. Multiple hemorrhagic foci and discoloration are present in the parenchymal organs, as in this lung and liver. Serosanguineous bicavital effusion is also present. (Courtesy of Dr. T. J. van Winkle, University of Pennsylvania)

Previous reproductive failure due to canine herpesvirus type 1 does not preclude future success.

DIFFERENTIAL DIAGNOSIS

Important diagnostic differentials for reproductive failure in pregnant bitches include infection with bacteria (*Brucella canis*, coliforms, *Streptococcus* spp), viruses (minute virus in dogs, canine distemper), and protozoa (*Neospora caninum*, *Toxoplasma gondii*).

DIAGNOSIS

CHV1 infection can be suspected whenever compatible clinical findings occur. Hematologic and biochemical investigations are of limited value. Affected adults have nonspecific changes. In clinically affected neonates, marked thrombocytopenia is uniformly present.

Serodiagnosis

Serologic testing has been the traditional method of diagnosing CHV1. This approach can be confounded because the virus is poorly immunogenic. After a dog has been exposed to CHV1 and possibly had an abortion, titers rise and fall rapidly (i.e., within 4 to 8 weeks) and have been estimated to last no more than 60 days after exposure,[4] although titers have reportedly persisted for up to 2 years.[27] CHV1 antibody titers are low, ranging from 1:2 to 1:32. Any titer greater than 1:2 is diagnostically significant when associated with suggestive clinical signs such as unexplained fetal loss or spontaneous late-term abortion. In the absence of clinical signs, a seropositive result is a reliable indication only of exposure, although latency can be presumed.

To facilitate diagnosis by this method, paired serum samples should be taken 10 to 14 days apart and refrigerated until assessment. A fourfold rise in antibody titer has been shown to be indicative of active infection.

Virus Isolation and Fluorescent Antigen

Following acute CHV1 infection, virus isolation is possible for 2 to 3 weeks. In previously exposed, recovered adults, viral growth is restricted to mucosal surfaces of the oral cavity, genitalia, and upper respiratory tract. Samples should be refrigerated for storage and transport and freezing avoided. Virus recovery is positive confirmation of infection. Suitable samples in live animals include nasal and vaginal swabs.

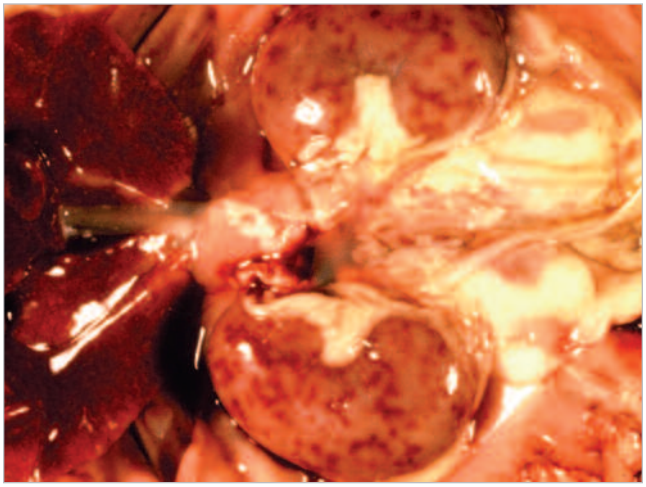

Figure 3. Renal hemorrhage. A consistent necropsy finding in infected neonates is multiple subcapsular renal ecchymoses. (Courtesy of Dr. T. J. van Winkle, University of Pennsylvania)

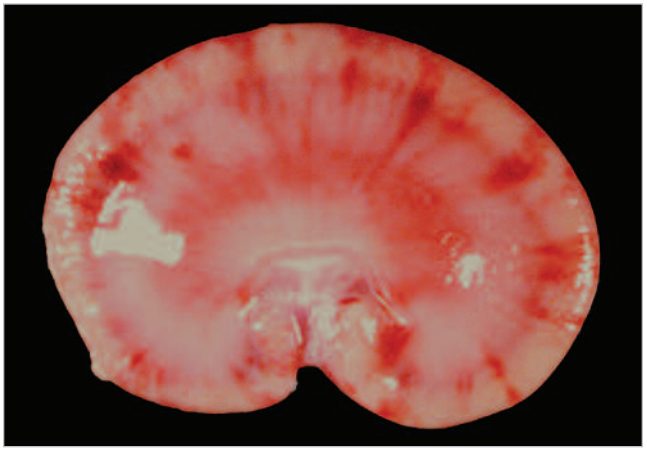

Figure 4. Renal hemorrhage. Sagittal section of a neonatal kidney reveals streaking hemorrhages radiating from the renal pelvis. (Courtesy of Dr. T. J. van Winkle, University of Pennsylvania)

Fetal and Neonatal Necropsy

Necrotic foci with inclusion bodies are characteristic of CHV1 infection and occur in multiple sites.[34] Prominent multifocal ecchymotic hemorrhage in the liver, lungs (Figure 2), and kidneys (Figure 3) is a regular gross finding. On a cut surface, radiating hemorrhages from the renal pelvis are present in the kidneys (Figure 4). Intestinal serosal surfaces may also be affected. Serosanguineous effusion of both pleural and peritoneal cavities is common. Necrosis and hemorrhage of the spleen, lymph nodes, and adrenal glands are present, often with splenomegaly and lymphadomegaly. The lungs are edematous, with the larger airways of neonates filled with frothy fluid.

From aborted fetuses and neonates, whole virus or viral antigen is recoverable from the vascular endothelium, liver, adrenal glands, lungs, spleen, kidneys, and lymph nodes. Fresh-chilled samples of these tissues should be collected.

* * *

Histopathology of formalin-fixed tissue samples should include the liver, spleen, kidneys, lungs, adrenal glands, pancreas, intestine, and heart. Multifocal necrosis is a prominent finding. Intranuclear inclusion bodies are common findings. They have been characterized variably in the literature as basophilic to weakly acidophilic,[35] depending on the stage of infection and fixation method.[27] Central nervous system lesions include nonsuppurative meningoencephalomyelitis, ganglioneuritis, and retinal dysplasia. Viral antigen is detectable by immunohistochemistry in a wide range of tissues. Necrosis may be visible grossly on fresh placenta as small gray–white foci. The placenta is an important diagnostic tissue but is often unavailable because of ingestion by the bitch.

TREATMENT

Once CHV1 infection is clinically apparent, treatment of infected puppies is unsuccessful because of the fulminant nature of the disease. Likewise, raising the environmental temperature of individual affected puppies does not alter the course of the disease. Mortality may be reduced in outbreaks by intraperitoneally administering serum from a previously affected bitch. A single 1- to 2-ml dose is sufficient.[27]

Male-to-female venereal contact is not a significant means of viral transmission.

Acyclovir is a guanosine analog commonly used in treating herpesviruses in humans. As with many antivirals, acyclovir targets steps in virus replication, specifically the action of viral DNA polymerase. Acyclovir is

CHV1 Vaccination

A commercial subunit vaccine is now available in Europe for active immunization of pregnant dogs. Eurican Herpes 205 (Merial) has been shown to improve birth weight and weaning rate and to reduce neonatal death from CHV1. Some evidence exists that litter size is also improved, suggesting a protective effect on fetuses.

The first vaccination should coincide with breeding, with a second 6 to 7 weeks later. Both vaccinations must be repeated with each pregnancy. High levels of protective antibody are passed via the colostrum. Latently infected females can also be vaccinated. The vaccine does not interfere with virus isolation or PCR-based diagnostics.

selectively uptaken by infected cells and phosphorylated by viral thymidine kinase to the active form. Modifying viral metabolism to avoid using this enzyme provides a means for viral resistance to this drug. The following is more clinically significant: The latent phase characteristic of herpesvirus infections does not involve active viral replication and is not amenable to such chemotherapy. Therefore, with currently available medications, eradication of persistent infection is not feasible.

There have been anecdotal reports of maternal therapy for neonatal prophylaxis. Treating affected litters has also been reported. Once clinical signs are present, however, infected neonates have a grave prognosis and will likely have residual neurologic and myocardial deficits if they survive.

CONTROL

CHV1 is relatively labile in the environment. It is inactivated by exposure to most common disinfectants. It cannot replicate at normal canine body temperature (>99.3°F [>37.4°C]) and is inactivated at 68°F (20°C).

It is impractical to attempt to eliminate the virus from a known infected canine population. Because of the stress-related nature of viral recrudescence, shedding, and susceptibility, animal management is an important means of control. Introducing any new individual to a breeding kennel should involve a period of quarantine and acclimatization to minimize the stress associated with a new social setting. Isolating all pregnant dogs during peak susceptibility (i.e., 3 weeks before to 3 weeks after parturition) is advisable.

PREVENTION

Following the report of an experimental CHV1 vaccine,[36] an inactivated vaccine became commercially available in Europe (see box on this page). This product is not available in the United States. Modified-live and inactivated vaccines for cats have been available for a number of years, but these vaccines do not protect against infection or establishment of viral latency. The virus replicates optimally at subnormal canine body temperatures. Neonates are unable to thermoregulate to adult levels, and adequate fever production is not possible. As a result, cell-mediated immunity is compromised. Adequate nutrition and temperature control of neonates to maintain normothermia are therefore imperative in situations in which the virus has been previously documented.[33]

FUTURE DEVELOPMENTS

Paradoxically, the infectious characteristics of CHV1 may turn out to be useful. Using CHV1 as a live viral vector for a rabies glycoprotein has been investigated.[37] Experimental inoculation with recombinant CHV1 expressing an *N. caninum* surface protein successfully induced IgG antibody to *N. caninum*.[38] Clinical signs associated with CHV1 infection were not seen, and the virus was not detected. This has important implications for developing a vaccine against *N. caninum*.

The trigeminal and lumbosacral ganglia are epidemiologically important sites of latency and recrudescence.

CONCLUSION

CHV1 infection has been documented to be more widespread in the canine population than once thought. Prevalence has been estimated to be 6% to 88%, depending on the nationality and husbandry of the population. Although latent infection is the most common manifestation, clinical signs ranging from mild vesicular genital lesions to fulminant neonatal sepsis may result.

With respect to canine reproductive failure, late-term abortion is the most common presentation. As with other members of the α-herpesvirus subfamily, the pathology of CHV1 centers on infection of the vascular endothelium of the uterus, placenta, and fetus. Viral translocation across the placenta, resulting in characteristic fetal vasculitis, edema, necrosis, and hemorrhagic body cavity effusion, is then able to occur.

Control of disease and prevention of infection involves avoiding viral exposure for naive gravid bitches; minimizing environmental, physiologic, and social stressors; and maintaining a standard of neonatal husbandry that ensures adequate body temperature and nutrition.

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1. Recrudescence of CHV1 infection has been noted with
a. immunosuppressive therapy.
b. altered social environment.
c. onset of proestrus in females.
d. all the above

2. Which herpesviruses are most important in veterinary medicine?
a. α
b. β
c. γ
d. all of the above

3. CHV1 antibody titers
a. reliably persist for an extended period.
b. rise to a high level.
c. rise and fall slowly.
d. are significant at low levels when accompanied by suggestive clinical signs.

4. In the absence of clinical signs, a positive CHV1 antibody titer
a. indicates active infection.
b. is a reliable indication only of CHV1 exposure.
c. is a rare finding in an adult dog.
d. gives no indication regarding the likelihood of latent infection.

5. Regarding the various α-herpesviruses, ability to cause abortion is likely associated with
a. genital lesions.
b. production of virokines.
c. leukocyte-associated viremia.
d. mucosal infections.

6. _____ is unusual among α-herpesviruses because it results in high mortality in a wide host range.
a. FHV1
b. BHV1
c. CHV1
d. SHV1

7. Latent CHV1 has not been found in
a. serum.
b. sensory ganglia.
c. tonsillar tissue.
d. the parotid salivary gland.

8. Regardless of the route of infection, all dogs shed virus via _____ during acute infection.
a. urine
b. semen
c. vaginal discharge
d. nasal mucosa

9. Which statement regarding CHV1 is correct?
a. It is environmentally resistant.
b. It replicates rapidly at adult canine body temperatures.
c. It resists most common disinfectants.
d. It is inactivated at 68°F (20°C).

10. Once neonatal clinical signs are apparent in a breeding colony,
a. raising environmental temperatures above normal adult canine levels is beneficial.
b. treatment with antivirals is curative.
c. treatment is unsuccessful.
d. attempts should be made to eliminate the reservoirs of latent infection in adults by using antivirals.