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EQUINE HERPESVIRUS AND NEUROLOGIC DISEASE

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Summary

Equine herpesvirus type 1 (EHV-1) myeloencephalopathy may occur with or without concurrent outbreaks of the respiratory and abortive forms of EHV-1 infection. Horses become infected by exposure to animals shedding the virus or via reactivation of latent EHV-1. Diagnosis is based on history, clinical examination, viral isolation, and serum antibody titers. In the face of an outbreak, isolation strategies aimed at decreasing spread of the infection should be implemented as soon as possible while treatment options are mainly supportive. Appropriate vaccination protocols and management strategies help decrease the likelihood of outbreaks of EHV-1 infection.

Introduction

Equine herpesvirus type 1 (EHV-1) and type 4 (EHV-4) are members of the Alphaherpesvirinae subfamily, genus Varicellovirus. EHV-1 is a major cause of abortion in mares whereas EHV-4 mainly causes respiratory disease (rhinopneumonitis) in young horses. In addition, EHV-1 is responsible for neonatal mortality and neurological disease in a small proportion of horses. In rare cases, EHV-4 may cause abortion, neonatal disease and neurologic disease. Currently, there are no reliable genetic markers available to differentiate between EHV-1 isolates responsible for abortion, respiratory or neurologic diseases. Both EHV-1 and EHV-4 are enzootic in most equids worldwide. Most horses > 2 years of age (80-90%) have detectable antibody titers to EHV-4 but seroprevalence for EHV-1 is lower.

Epidemiology

The neurologic form of EHV-1 infection causes a myeloencephalopathy that has been recognized in many countries around the globe. Despite the widespread distribution of EHV-1 infections, the neurologic form of the disease is rare. Cases of neurologic EHV-1 infection are usually observed during outbreaks of abortion or respiratory disease. Some neurologic cases have occurred without other clinical manifestations of EHV-1 infection. Up to 50% of infected horses become latent carrier of the virus for life, therefore constituting a large reservoir of horses potentially shedding EHV-1. Latent infections explain why some outbreaks of EHV-1 infection may occur in closed herds in the absence of exposure to new horses. A susceptible horse may become infected because of exposure to respiratory secretions from an actively infected horse or to a fetus and fetal membranes aborted from a mare. Alternatively, stressful episodes or corticosteroid treatments may reactivate the virus in latently infected horses and result in EHV-1 infection. The virus may remain infective in the environment for up to 42 days. Infected horses may shed EHV-1 in nasal secretions for as long as 14 days. The route of entry for EHV-1 is the upper respiratory mucosa via direct contact or by inhalation of aerosolized secretions containing the virus. The incubation time for the neurologic form of EHV-1 is 6-10 days and horses that suffered prior infection are at higher risk of developing neurological signs as compared to naïve horses. Pregnant and nursing mares may also be at increased risk but foals are affected less often and usually exhibit less severe clinical signs. Morbidity rate may vary between single cases on premises up to 90% of exposed horses. Mortality rate may range between 0.5% and 40% of in-contact horses.

Clinical signs

Prior to the first case of neurologic disease, there is often a history of respiratory disease, abortion, fever, inappetence, hindlimb edema, or foal disease (e.g. diarrhea, pneumonia) within the previous 2 weeks. In many cases, neurological deficits such as ataxia are the first signs observed. Clinical signs vary from mild ataxia to complete paralysis of the hindlimbs and recumbency. Tail and anus hypotonia, and bladder paralysis with incontinence are frequently noted. Neurologic deficits are usually bilaterally
Symmetric but not always and hindlimbs are generally more severely affected than front limbs. Skin sensation is usually preserved as well as flexor and perineal reflexes. Affected stallions may present with hindlimb edema, reduced libido, testicular swelling, penile flaccidity, and paraphimosis or repeated erections.(1; 6) Bladder paralysis may result in complications such as urine scalding and cystitis. Signs of uveitis with hypopyon and respiratory and gastrointestinal disease have been reported in foals during an outbreak of EHV-1 myeloencephalopathy.(6) In severely affected horses, progression is usually rapid with paralysis and recumbency developing within the first 24-48 hours.(6; 7). Mildly affected horses frequently stabilize quickly and recover fully within days to weeks.(8)

Pathogenesis and pathology:

EHV-1 expresses a marked endotheliotropism and not neuritropism, although viral antigen may be found in neurons and astrocytes.(8) Infection starts by virus replication in the upper respiratory epithelium and is followed by dissemination to lymph nodes via infected dendritic cells and macrophages. Further dissemination of EHV-1 infection occurs by entry of virus-infected mononuclear leukocytes into the blood stream (i.e. viremia).(2) Then replication of the virus in endothelial cells results in vasculitis and may lead to thrombosis of small blood vessels and secondary ischemia, axonal swelling, malacic foci and hemorrhage and ultimately, myeloencephalopathy.(1) Vascular lesions in the spinal cord and brain of affected horses are consistent with an immune-mediated vasculitis rather than with damage induced by direct viral replication. Gross lesions of the central nervous system may include scattered hemorrhages on the surface of the dura mater and in the parenchyma of the brain and spinal cord.(1; 7) Histology reveals perivascular mononuclear cuffing, thrombosis and necrosis of small blood vessels, hemorrhage, axonal swelling, and malacic foci with the most severe lesions usually located in the brainstem and spinal cord white matter. Inflammatory and hemorrhagic lesions in the respiratory tract are common. Pregnant mares may show vasculitis and areas of necrosis of the endometrium.

Diagnosis

Differential diagnoses for EHV-1 myeloencephalopathy include mainly equine protozoal myeloencephalitis, cervical vertebral stenotic myelopathy (wobbler syndrome), trauma, viral encephalitides, and neuritis of the cauda equina. Historical information is essential to raise the suspicion of EHV-1 infection. A history of respiratory disease or abortion in a herd followed by neurologic deficits including ataxia and urinary incontinence would be consistent with EHV-1 infection. Collection of cerebrospinal fluid (CSF) often yields a xanthochromic sample with elevated protein concentration (>100 mg/dl). Otherwise, CSF cytology is usually normal. Antibodies to EHV-1 detected in CSF result from leakage across the blood-brain barrier, however it may also be secondary to iatrogenic blood contamination. Isolation of the virus from CSF is rarely achieved. Alternatively, isolation of EHV-1 from nasopharyngeal swabs or blood in anticoagulant (20 - 50 ml in heparin, EDTA, or citrate) should be attempted. Samples have to be shipped on ice in order to preserve EHV-1 viability. Swabs must be placed in a fluid transport medium with antibiotics. Optimal time to sample is during febrile episodes prior to neurologic signs. Some animals, especially foals, may be viremic for weeks to months after infection.(6) However, by the time horses display neurologic signs, viral shedding is already declining. EHV-1 specific PCR is available in some laboratories and is more sensitive than virus isolation, but detection of latent virus instead of viremia can not be excluded.(8) A presumptive diagnosis may be reached by demonstrating a markedly elevated serologic titer in an acute sample or an increase in titer (≥ 4 fold) between acute and convalescent samples taken 1 to 3 weeks apart.(1) However, the diagnosis may be complicated by the fact that antibody titers often peak by the time horses show neurologic signs. Taking serum samples from horses in contact with affected animals may help demonstrate prior infection and the extent of the spread.(6) The 3 most common detection tests of serum antibodies are virus neutralization (VN), complement fixation (CF) and ELISA. Recent evidence suggests that ELISA tests can differentiate between EHV-1 and EHV-4 infections, whereas cross-reactivity between SN and CF tests may confound the results.(9) Samples collected at post-mortem should include brain, spinal cord, spleen, thyroid, lung, and endometrium. Detection of viral antigens by immunofluorescence or immunoperoxidase methods is more sensitive and rapid than virus isolation.(10)
Management strategies and treatment

First and foremost, strict isolation protocols should be implemented as soon as a presumptive diagnosis of EHV-1 is made. Isolation protocols are aimed towards prevention of the spread of the virus among horses by separating aborting mares, sick newborns and any horse exhibiting fever, nasal discharge, or gait deficits from the herd.(5) All movement on and off the premises should cease and strict regulation should be put in place concerning visitors.(8) Recently foaled mares and pregnant mares should be divided into small groups as soon as possible.(6) Aborted fetus and fetal membranes should be sealed in plastic bags and submitted to a diagnostic laboratory. Sanitary barriers should be put in place around isolated horses including the use of disinfectants, protective clothing, disposable gloves, and waterproof footwear. Cleaning of the facilities and equipment should be conducted with water and detergent to remove organic debris. This should be followed by disinfection with germicidal compounds. Phenolics are recommended in horse facilities because of their efficacy in the presence of organic matter, however hypochlorites (bleach) and quaternary ammonium compounds may be used on cleaned surfaces.(11) Iodophores but not chlorhexidine may be used as a skin antiseptic. Equipment should not be shared between isolated animals and the rest of the herd. All horses should be observed daily for signs of EHV-1 infection. Vaccination of horses recently exposed to EHV-1 is not recommended because of the possibility of worsening of neurological signs.(5) However, vaccination of horses surrounding the affected premises should be considered. Unaffected horses should be kept isolated for a minimum of 3 weeks after recovery of the last clinical cases.(5; 8) Pregnant mares should not be moved away from the farm until after foaling. The main therapeutic goals are reducing stress (e.g. stop breeding or training activities), providing supportive care, treating CNS inflammation and preventing secondary complications. Fluid therapy and nutritional support should be provided to horses with inappetence or unable to access food and water. A laxative diet is recommended and evacuation of the rectum may be necessary. In cases of bladder paralysis, manual evacuation per rectum or bladder catheterization should be performed at least twice daily. Broad spectrum antibiotics are recommended to avoid cystitis and other secondary infections (e.g. potentiated sulfonamides, penicillin/gentamycin). Horses too ataxic to stand may be maintained in slings to avoid pressure necrosis of the muscles and other complications of recumbency. Ataxic horses that are able to stand on their own may have a better prognosis if turned out on pasture.(6) Non-steroidal antiinflammatory drugs (e.g. flunixin meglumine 1.1 mg/kg IV q 12 hours, phenylbutazone 2.2-4.4 mg/kg PO q 12-24 hours) and dimethyl sulfoxide (DMSO; 0.5-1 g/kg IV as 10-20 % solution, q 24 hours) are indicated for the treatment of CNS inflammation. The use of corticosteroids is controversial because their immunosuppressive effects may result in prolonged viremia however, they may prevent immune-mediated vascular damage. Therefore, if corticosteroids are used, the course of treatment should be brief (2-3 days) and use short-acting drugs (e.g. prednisolone acetate 1-2 mg/kg/day; dexamethasone 0.05-0.1 mg/kg, q 12 hours). Antiviral drugs such as acyclovir (10 mg PO, 3 - 5 times per day) may be beneficial, however clinical trials have not established its efficacy for EHV-1 myeloencephalopathy.(2; 12)

Prognosis

Horses showing neurologic deficits but remaining standing usually improve within a few days. Horses with severe deficits may take months to recover and most will not return to normal.(6) Horses that become recumbent for more than 24 hours have a poor prognosis. However, the decision to euthanatize a recumbent animal should not be made too quickly because some may recover after being recumbent for days provided they were given appropriate nursing care.(1) Return of urinary control often precedes gait deficit recovery but it is not uncommon for horses to be left with neurologic deficits.

Prevention

Strategies include prophylactic immunization and preventative herd management practices.(2) Currently marketed vaccines are only labeled against EHV-1 and EHV-4 abortion and respiratory diseases. A protective effect of vaccines against EHV-1 myeloencephalopathy has never been demonstrated and severe outbreaks of EHV-1 abortion, neonatal foal death, and neurological disease may occur despite regular vaccination with currently available products.(5) Nevertheless, proper herd vaccination and management practices have resulted in a dramatic decline in abortion storms among Kentucky broodmares over the last 40 years.(5) Also, vaccination attenuates clinical severity of
respiratory disease and duration a viral shedding. Recent evidence suggest that EHV-1 anti-abortion vaccines provide a greater immunity as compared to EHV-1 respiratory vaccines. (13) Furthermore, vaccines should contain both EHV subtypes in order to maximize immunization. (14) Because most foals have colostrum-derived antibodies to EHV-1 and EHV-4, vaccination should be initiated when they are 5-6 month of age with the first 2 doses administered 1 month apart and a third booster 8-12 weeks after the second dose. Horses at high risk (yearlings, horses in training, racing and showing) should receive booster doses every 4 months. Pregnant mares should be immunized with an inactivated vaccine according to label instructions (usually 5, 7, and 9 months of gestation). Breeding stallions should be vaccinated twice a year with one dose before the breeding season. Promising experimental studies have demonstrated that a single dose of intranasal live EHV-1 vaccine (strain C147) administered to adult horses is protective against abortion and respiratory disease caused by EHV-1 infection for up to 6 months. (15; 16) In another experimental challenge model, the same intranasal vaccine also afforded protection of young foals with maternally-derived antibodies against febrile respiratory disease and virus shedding. (17) Preventative management strategies are based on 1) segregation of horses into small groups of similar age, gestation status, and use, 2) maintenance of each group as an isolated unit, physically separated from the other units and 3) reduction of the stress by providing proper nutrition, parasite control, and avoiding long trailing rides or frequent introduction or removal of horses from established groups. (2) New animals should be isolated for 3 weeks before being allowed into the herd. (5)

References

