EHV-1 Controversies

What are the areas of disagreement on, or incomplete understanding of, the neurologic form of equine herpesvirus-1?

BY KIMBERLY S. BROWN

There are several diseases that have clinical signs of neurologic dysfunction. However, in cases of equine herpesvirus-1 myeloencephalopathy (the neurologic form), these neurologic signs reflect diffuse multifocal hemorrhagic vasculitis and thrombosis, meaning the virus has damaged the lining of the blood vessels in the central nervous system, leading to inflammation and clots. Pam Wilkins, DVM, MS, PhD, Dipl., ACVIM, ACVECC, of the University of Pennsylvania's New Bolton Center, desribed these pathologis at a meeting hosted by the C.L. Davis Foundation and the American Association of Veterinary Laboratory Diagnosticians on Equine Herpesviral Diseases. The meeting was sponsored by Fort Dodge Animal Health and was held just prior to the start of the December 2007 convention of the American Association of Equine Practitioners.

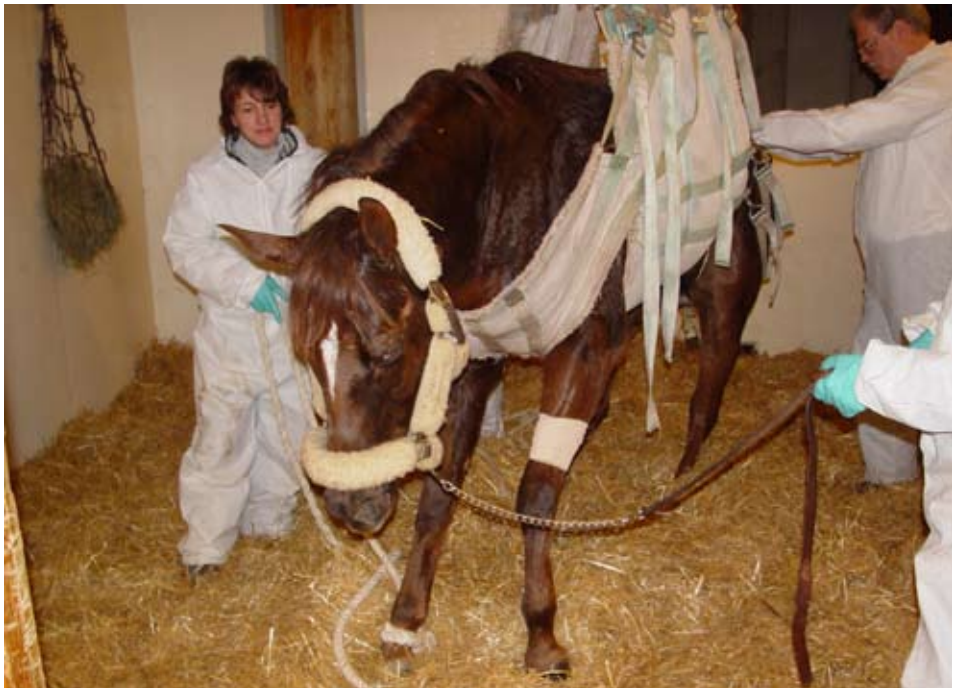
Wilkins said EHV-1 myeloencephalopathy usually starts with a sudden onset of neurologic signs, early stabilization of signs, and there may have been recent history of fever, abortion, or respiratory signs in animals in contact with,or residing on the same facility as, the affected horse.

The neurologic form of EHV-1 "initially was thought to be an immune-mediated vasculitis … wrong," stated Wilkins to the group of veterinarians and diagnosticians. "Animals with neurologic signs are actively infected, probably shedding (virus), and a risk to other horses. Big lesson we learned starting in the 90s."

She said equine herpesvirus myeloencephalopathy (EHM) clearly differs from herpesvirus-associated neurological disorders in other species in that there is "no clear evidence of direct neuronal invasion or damage due to the virus itself."

A key point in Wilkins' talk was her explanation of how neurologic signs are caused with EHV-1. She said when EHV-1 infects a circulating white blood cell (thought to be a T lymphocyte), then that cell interacts with an endothelial cell (a cell that lines blood vessels) and the virus is transferred to the cytoplasm of the endothelial cell. While in the endothelial cell the virus replicates and damages the cell. This causes a spinal "stroke" because of subsequent vascular occlusion and lesions in the spinal cord.

"That explains the acute onset of neurologic signs," said Wilkins. "(It is) useful to use that analogy to explain to lay persons as to why it (neurologic signs) happens so quickly. The clots cause the neurologic problems."



COURTESY DR. STEVE REED

EHV-1 myeloencephalopathy usually starts with a sudden onset of neurologic signs, early stabilization of signs, and caretakers might choose to sling the horse, as shown here, and focus on supportive care.

Herpes is Forever

Wilkins said latency as it pertains to herpesviruses used to be debated … "herpes is forever!" she exclaimed.

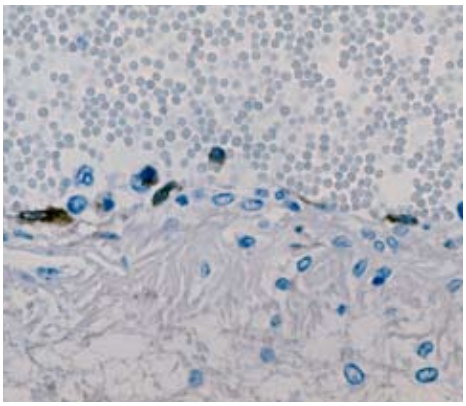
Latency is when a virus lives in a host and remains "hidden" or at such a low level that the host does not mount a defense against the virus. Many horses are latently infected with the equine herpesviruses secondary to infection, frequently clinically silent, that they acquired when they were younger. Then times of stress—or even certain medications—can cause the immune system to become less efficient. During those times the virus can reactivate and begin replicating, causing clinical signs in the host or reproducing and shedding from the host in enough numbers to be spread to other animals.

Controversies

Treatments

"Dexamethasone and prednisolone administration (both are steroids) can cause reactivation of latent infection," said Wilkins, who added that reactivation of the virus can also occur with administration of interleukin-2 (IL-2), a compound that induces proliferation of immune cells and chorionic gonadotropin (a hormone) in experimental models.

"We use to treat these horses (neurologic cases) with corticosteroids … (now) I only use them at low, anti-inflammatory doses," said Wilkins. At higher doses, corticosteroids such as dexamethasone and prednisolone act as immunosuppressants, probably an undesirable effect in active equine herpesvirus infections.



COURTESY DR. STEVE REED

Immunohistochemistry labeling equine herpesvirus type-1 (EHV-1) in endothelial cells. Dark stained (golden brown) cells are endothelial cells, red blood cells are contained within the venule (small vein) at the top of the image.

"DMSO (dimethyl sulfoxide), in my opinion, smells bad and doesn't do much," said Wilkins in discussing other anti-inflammatory tools that have been used to treat horses with EHV-1 myeloencephalopathy.

However, Steve Reed, DVM, Dipl. ACVIM, now of Rood and Riddle Equine Hospital in Lexington, Ky., and formerly of The Ohio State University, said he still uses DMSO to treat horses with EHV-1 myeloencephalopathy.

Wilkins said horses have been treated with interferon gamma (a glycoprotein produced by T lymphocytes that prevents virus multiplication) in one study, with no observed positive effect.

"Acyclovir and valacyclovir (given orally this becomes acyclovir in a horse's circulation) have been tried," said Wilkins. "There is controversy whether it works. Acyclovir can inhibit replication of EHV-1 virus, but not all herpes are equally sensitive to the drug."

Wilkins discussed reports describing use of acyclovir in management of equine herpesvirus-1 myeloencephalopathy outbreaks in Virginia and in a retrospective study from Cornell in the 1990s; researchers also used valacyclovir in Florida and Colorado research. "No clear-cut benefits have been established in those reports," noted Wilkins. However, she said veterinarians involved in 1 22003 outbreak at Findlay University in Ohio (see page 19 for more information) felt the medication helped.

When do we use these treatments? "In sick horses they possibly decrease viral shedding," said Wilkins. "The goal of using these drugs is to reduce morbidity (illness) and mortality (death) in patients and known exposed animals. We need to determine how to use antivirals responsibly and appropriately in order to protect their usefulness in future, and minimize development of resistant virus strains.

"There are no demonstrated effective treatment protocols now; most treatments are prescribed as prophylactic or supportive therapies," she said. "The current antiviral debate seems to revolve around dose and route, potential toxicity, efficacy, and their use as prophylaxis."

Route of administration is particularly important, as if acyclovir is given intravenously (IV) at too great a concentration or too rapidly, "you can drop the horse like a stone." This means that an adverse reaction of acute collapse (in the reported instances of this, the horses have all recovered from the adverse reaction) has been seen with IV acyclovir given at high concentration in 20 minutes or less. "The recommendation is that if the IV route of administration is chosen, the concentration of the administered solution should be low and it should given as a slow infusion over one hour," she warned. "To date, no adverse reactions have been reported when these recommendations have been followed."

Prevention

Vaccination against EHV-1 myeloencephalopathy is controversial. "No vaccine is labeled as protective against EHM," said Wilkins. "The virus lives intracellularly. Cell-mediated immunity is likely to be the most important."

"Does frequent vaccination (against EHV) predispose horses to disease?" she asked. "I think it's a crap shoot and doesn't play a strong role. Findlay did have some indicators (that pointed to worse cases in 'overly-vaccinated' horses), but that needs to be looked at some more."

She reminded the audience that antibodies can't get to this virus very easily, so even high antibody levels might not mean protection.

ANNE M. EBERHARDT

Horses affected with EHV-1 should be isolated promptly, and there should be no transport of horses on or off the property until three weeks after the resolution of acute clinical signs, and until testing shows virus transmission is no longer occurring.

Control of Outbreak Controversy

Wilkins explained that the source of an outbreak can be a new horse introduced to a herd, or reactivation of a latent infection.

The goal of management in an outbreak situation is to control spread of the virus via infectious aerosols, direct contact, and by reducing stress-inducing reactivation or additional latent infections.

"Affected animals need to be isolated promptly!" she stressed.

Wilkins reminded the audience that multiple problems can occur in a single horse, making diagnosis difficult, which can sometimes lead to spread of the EHV-1 virus when proper management protocols are not followed with a neurologic horse.

"Horses can have EPM (equine protozoal myeloencephalitis) and herpes concurrently; it's not common, but it does happen," she stated.

"If (a horse) sheds herpesvirus, then it can be a risk to other horses," Wilkins said. "In-contact horses should be isolated in one or more small groups and observed. Pregnant mares should be isolated until they foal."

Wilkins said there be no transport of horses in or out of the property "until three weeks after the resolution of acute clinical signs in the last affected case *and* until testing shows virus transmission is no longer occurring."

She reminded the audience that at Findlay, "they saw a second wave of the outbreak; Maryland had a third wave of outbreak.

"You must be vigilant," she stressed. "Don't be in a hurry to release these horses."