More thoughts on EHV-1

Dr. Christine King

It's May 23rd, 2011. We're now more than 2 weeks into the latest outbreak of neurologic disease caused by equine herpes virus type 1 (EHV-1), and I wanted to share some additional thoughts on this disease.

First, a quick reminder:

- the virus is EHV-1
- the neurologic disease it occasionally causes is EHM, for Equine Herpes Myeloencephalopathy (= disease of the spinal cord and brain)

But it's important to realize that EHV-1 and EHM are not the same thing, and these terms are not interchangeable. *Most horses with EHV-1 do not have, and never will have, EHM.*

There has been a lot of research on EHV-1 in the past decade, but still we have more questions than answers. One of the most pressing questions is why only a few horses with EHV-1 develop EHM. What are the factors involved in individual susceptibility to EHM?

Equine herpes primer

Equine herpes viruses, particularly EHV-1 and EHV-4, are very common in horses. In fact, it would not be too great a stretch to use the word "ubiquitous." Most horses are first infected as young foals, picking up the virus from their mothers, other broodmares on the farm, or other foals. The virus establishes long-term residence in the young horse, remaining probably for life in most cases, being dormant most of the time and reactivating only during periods of stress.

This common characteristic of herpes viruses is called latency: the infection is latent or dormant most of the time and active only occasionally. If you get cold sores when you're stressed or sick, then you'll be very familiar with this dynamic, as cold sores are caused by a human herpes virus.

Population studies in horses suggest that at least 60% of horses, and with the more sensitive diagnostic methods, almost 90% of horses in some populations, have at least one strain of EHV-1 in residence. A recent statement by the American College of Veterinary Internal Medicine included this telling remark: "For practical purposes, clinicians should presume that the majority of horses are latently infected with EHV-1."

And yet, despite the prevalence of this virus, *neurologic disease* caused by EHV-1 is very uncommon. The outbreaks of EHM get a lot of attention when they occur, but given the size of the horse population here in the US and how much horses are moved around the country these days for competitions, breeding, sale, family relocation, etc.—for such a common virus, these outbreaks of EHM are strikingly *un*common.

Also, during an outbreak, the incidence of EHM in exposed horses typically is less than 10%.

For example, although we're only midway through this latest outbreak, the incidence of EHM in the more than 1,000 horses exposed either at the show or by horses returning home from the show is currently less than 3%. We're not done with this outbreak yet, but we've likely seen the bulk of the EHM cases already, so although that figure will probably increase before all is said and done, it is not likely to climb out of the single digits. As a point of comparison, the incidence of fetal loss during outbreaks of EHV-1 abortion in broodmares may be over 50%.

EHV-1 strains

A lot of attention has been paid to the different strains or genetic variants of EHV-1 and their disease potential. Here's a brief summary of what we know:

- there are several different strains or genetic variants of EHV-1, but they have vastly more characteristics in common than they have differences, which is why they're all called EHV-1
- all strains of EHV-1 are primarily *respiratory viruses;* they first invade and multiply in the cells lining the airways, which is also how they are usually spread from horse to horse—in nasal secretions, and less often in a cough or sneeze
- although EHV-1 is ubiquitous in the horse population, we only occasionally see clusters of either abortion or neurologic disease; and seldom, if ever, do we see both at the same time
- with regard to its ability to cause either abortion or neurologic disease, there is one primary genetic variant of EHV-1 that I'll simplify to N and D strains
- the N strain is by far the most common variant, accounting for at least 80%, and in some populations up to 95%, of all EHV-1 strains; it is also the one most strongly associated with abortion
- the D strain is much less common, accounting for between 5% and 20% of all EHV-1 strains; it is the one most strongly associated with neurologic disease, being responsible for 75–85% of all cases of EHM
- however, it is possible for the N strain to cause neurologic disease and the D strain to cause abortion
- most horses have either the N or the D strain, but a few are co-infected with both strains

But here's where it gets really interesting. There is some evidence that the N variant is the more recent adaptation this virus has made to the various selection pressures it has experienced over its generations. Evidently, the N variation provides some selective advantage over the D strain. For one, the N strain causes less harm to its host.

The vast majority of cases of EHV-1 infection are seen in young horses, especially yearlings and 2-year-olds just starting in training and competition. In these horses it causes its primary disease: *rhinopneumonitis,* or inflammation of the upper and lower airways (rhino = nose; pneumo = lungs). Hence its common name, "rhino." It causes usually mild, flu-like symptoms,

and unless it is complicated by some other infection (e.g. bacterial pneumonia), the recovery rate is 100%.

Similarly, in outbreaks of EHV-1 abortion in mares, the recovery rate is pretty much 100%. The incidence of fetal or neonatal death is high, but few, if any, mares die from EHV-1 infection during these outbreaks. And typically, the affected mares don't even show obvious signs of illness, other than spontaneous premature delivery or abortion.

In contrast, horses with EHM can be quite ill. A high fever is common at some point during the disease, and the neurologic signs can be quite severe, in some cases progressing to an inability to stand. The mortality rate, whether from natural causes or euthanasia, is at least 25% in horses with neurologic signs.

The D strain appears to be quite old. For example, it has been identified in a sample collected from a horse in 1941. In fact, there is some evidence that it may be the original genotype of EHV-1. In other words, the virus probably began as the D variant, but at some point and for some reason, it mutated to the N variant.

This mutation is not stable, meaning that it is not consistently inherited in subsequent viral generations. But that just lends weight to the speculation that this mutation is a positive adaptation, made to ensure the on-going survival of the virus in its host. Internal parasites face the same issue: it is not a good long-term survival strategy to kill one's host!

The fact that this mutation is relatively unstable suggests that the virus is keeping its options open. What further adaptations EHV-1 might make, both at this specific N/D gene site and at others, remain to be seen. In recent decades EHV-1 has had to contend with widespread and intensive vaccination practices. Immunostimulant use has also increased in young performance horses—primarily for the control of respiratory infections! So, to ensure its continued survival, this virus may have to adopt even more stealthier habits.

Vulnerability theory

Thus far, we've established that the less neuropathic N variant is the most common strain of EHV-1 now in circulation. That takes us partway in understanding why EHM outbreaks occur so infrequently and affect so few horses: the more neuropathic D strain is relatively uncommon.

But might there be more going on? And what is it about the D strain that makes it more likely to cause neurologic disease?

We don't yet know, but the possibilities include higher circulating levels of virus (i.e. greater degree of viremia) with the D strain, so greater potential for damage; and differences between strains in their ability to attach to the cells lining the blood vessels (endothelial cells) of the spinal cord and brain.

Yes, but *why the central nervous system* with the D strain? (And why the uterus and placenta with the N strain?) Why not other organs or tissues?

That's what really interests me: why certain cell types, tissues, organs, or body parts are affected and not others. Same for cancer as well as for infectious diseases, injuries, and pretty much any other medical condition. Why *there?* is the question I keep asking myself. What does

it mean that it's happening in one site or system and not another? And what does that mean for how we treat and prevent this disease?

I'm also fascinated by the concept that viruses are little more than genetic code. They primarily consist of relatively short strands of DNA or RNA—in other words, encoded information which directs the functions of a cell. For the most part, viruses are quite species-specific. They also tend to be quite organ- or tissue-specific. So, infection by a particular virus or a particular strain of a virus tells us something about the individual host's vulnerability.

Here are some things to ponder about EHV-1, particular in regard to EHM:

- EHV-1 primarily infects the cells lining the airways so that it can readily be spread from horse to horse, and thus preserve its existence over time. Life is geared toward survival of the individual and perpetuation of the species—i.e. continuation of that life form. When it comes to EHV-1, both its habits and its changes over time reflect this tenacity.
- EHV-1 hides out in white blood cells, lymph nodes, and in the trigeminal nerve, which is one of the major nerves that supply the face, including the lining of the nasal passages. From any of these locations, it can quickly reactivate and move into the airways whenever the body's defenses are compromised because of stress or illness. It is interesting that this virus evades the body's immune system by hiding out *inside* the immune system. It could only do that if the body's defenses were somehow compromised by stress, illness, or immaturity.
- EHV-1 secondarily infects the linings of the blood vessels in a couple of key sites—the uterus and placenta (causing abortion) or the spinal cord and brain (causing EHM). But why disease primarily occurs only in these organs or tissues is still a mystery. It could well be that these are the most vulnerable organs or tissues in that individual at that time. That certainly appears to be the case in pregnant mares...
- EHV-1 abortions occur mostly in the last trimester of pregnancy, when the fetus is growing rapidly and demands on the pregnant mare are increasing by the day. In other words, pregnancy, while a normal physiological process, is taxing on the system, much like strenuous exercise is both normal and taxing. There are also hormonal and immunological changes in the late-term pregnant mare that may further increase her vulnerability. Perhaps that's why the pregnant mare is vulnerable to EHV-1 disease and the uterus is the target organ.
- EHV-1 myeloencephalopathy (EHM) occurs mostly in young adult horses under the stress of training and competition. It occurs most often in busy boarding/training barns and at events such as the cutting horse show in Utah recently. Horses traveled from all over the country to attend that high-stakes event.
- The central nervous system is the generator of the body's locomotor processes. Whether movement originates with a conscious thought or an unconscious impulse, the directive is sent to the muscles which enact it via the nerves of the brain and spinal cord.

- The main signs of neurologic involvement in horses with EHM are weakness and incoordination (ataxia). In other words, the horse has less control over how his body moves, and even whether it moves under his direction.
- Metaphorically, this state represents *a crisis of self-direction and control* over how the horse responds to what's going on around him.
- It should therefore not surprise us that EHM occurs most often in stressed young performance horses who find themselves transported many hours or days to an event, confined in unfamiliar quarters, surrounded by strangers, and then required to perform at their peak – talk about lack of control!

Combine that with the small percentage of horses latently infected with a D strain of EHV-1, and we gain a better understanding of why outbreaks of EHM occasionally occur at these events and seldom, if ever, at home. From the data we have, it seems clear that horses can be latently infected with a D strain of EHV-1 for life and never develop EHM. It's not just about the virus. It's *never* just about the virus.

Back to the vulnerability theory, a viral infection shows us where we are most vulnerable. With EHM, it is the spinal cord and brainstem—the parts that are responsible for core functions of information processing and response; especially response. It is interesting that the herpes viruses of all types have a habit of latency, re-emerging during periods of stress (i.e. *increased vulnerability)* to show us where we need to shore up our boundaries and otherwise address our vulnerabilities.

So, what does this mean for the prevention of EHM? I would suggest that, in addition to good food, plenty of rest, loving social bonds, and all the other fundamentals of good health and well-being, we ought to be encouraging as much *self-determination, self-direction, and control* as possible for the individual horse under the specific circumstances. How you go about that will depend on your horse and your situation. But no matter how you accomplish it, if my theory is even partially correct, enabling your horse to feel a bit more in control of what happens to him will likely go a long way toward reducing his vulnerability to EHM.

Or, you could just vaccinate and cross your fingers ☺

Primary Resource:

Lunn DP, Davis-Poynter N, Flaminio MJBF, et al. Equine herpesvirus-1 consensus statement. *Journal of Veterinary Internal Medicine* 2009; 23: 450–461.

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