EPM Update

BY DR. CHRISTY CORP-MINAMIJI
STEPHANIE CHURCH PHOTOS

Few equine conditions cause as much consternation as equine protozoal myeloencephalitis (EPM). First reported in 1968, EPM represents both amazing scientific progress and extraordinary clinical frustration. Its causative agents are widespread in North America, and affected horses display neurologic signs such as ataxia (incoordination) and asymmetric atrophy (muscle wasting on one side of the body). However, the disease is sporadic and veterinarians cannot diagnose it definitively yet in the live horse.

So why is a disease that is one of the few treatable equine neurologic conditions and for which scientists have identified the causative organisms (now down to the genomic level) so frustrating? To address these questions, let's first take a look at the disease and these organisms, along with EPM's mechanisms of action, diagnosis, and treatment.

The Troublemakers

According to a 2009 Equine Research Coordination Group White Paper, a protozoon (single-celled parasite) known as *Sarcocystis neurona* causes an estimated 95% of EPM cases. Researchers have also identified another protozoal organism, *Neospora hughesi*, associated with some cases. While *S. neurona* and *N. hughesi* are "somewhat closely related," said Daniel Howe, a molecular parasitologist at the University of Kentucky's Gluck Equine Research Center in Lexington, the parasites' geographic distribution appears to be different. He says *N. hughesi* is "more common on the West Coast, with *Neospora*-positive samples seemingly pretty rare in the Midwest and East."

Like most other parasites, *S. neurona* develops through several life cycle stages during which it relies on various hosts. *S. neurona*'s final, or definitive, host is the opossum, which sheds the parasites when they reach their infective stages (sporocysts) in its feces. Intermediate hosts (including raccoons, armadillos, sea otters, skunks, and cats) become infected by eating food contaminated with the sporocysts. In true intermediate hosts (in which the parasite develops through several life cycle stages, as opposed to a "dead-end" host such as the horse) the sporocysts mature after several cycles to bradyzoites (another stage of maturity) that form sarcocysts in the muscle. The definitive host becomes infected by eating sarcocyst-infected muscle of one of these various intermediate hosts. The parasites reproduce in the opossum's intestine to produce the sporulated oocysts (the "egg" stage containing the sporocysts) the opossum then excretes.

Got that? Scavenging opossum eats parasite encysted in roadkill; parasites party in the opossum's intestines; and opossum poops parasite eggs. This, presumably, is

Diagnosing EPM is far from straightforward, so owners need to be vigilant checking a horse's central nervous and immune systems

where the horse comes in—and unfortunately, the horse is not a natural host for *S. neurona*. Sarcocysts do not encyst in the muscle; instead, parasite stages travel to and lodge in the brain and spinal cord.

A Little Anatomy Lesson

Everything that happens in the body, from eating to walking to breathing and even muscle development, depends on the appropriate relay of signals along nervous system pathways. Break one connection, and everything after that point goes awry.

A basic understanding of the horse's neuroanatomy is critical to understanding EPM simply because *S. neurona* can strike anywhere along the central nervous system (CNS). Working from front to back (nose to tail) of the horse's CNS, we see the forebrain, hind brain (brainstem) and cranial nerves, and spinal cord. Nerves then branch off from the spinal cord, flowing like minor tributaries throughout the body.

The forebrain regulates intrinsic and learned behaviors, vision perception, and sense of touch. The upper motor neuron system (UMN) encompasses parts of the forebrain and brainstem and is responsible for voluntary movement (that which the horse decides to do) and postural support against gravity. The brainstem regulates physiologic mechanisms such as body temperature, chemistry, pH, blood pressure, hydration, etc., as well as consciousness, some eye function, facial movements (chewing and swallowing), and trunk and limb coordination.

Information travels along the spinal cord in specific directions in specific regions, with upper motor neurons relaying information from the brain to lower motor neurons (LMN, nerves traveling from spinal cord to muscle) and the LMNs conveying the message to muscles and tendons.

But sometimes you don't have to take the message all the way to the boss—and it's faster if you don't. In the case of spinal reflexes, sensory neurons relay the message (pain, tickle, heat, etc.) to the spinal cord, then contact the LMN and then the motor neurons. Thus, as in the classic scenario from human biology class, the hand jerks away from the stove before the brain realizes the burner is glowing.

The Protozoa's Progression

Horses become infected with *S. neurona* by eating feed or drinking water contaminated with sporocyst-laden opossum feces. Yet, while many horses show immunologic evidence of exposure on blood tests, only a handful develop neurologic disease. And among those horses, the clinical signs and their progression vary widely.

Robert MacKay, professor of Large Animal Medicine at the University of Florida's College of Veterinary Medicine, said many variables could cause variation in EPM's progression and appearance among horses, including:

The longer the lag between the onset of signs of EPM and treatment, the poorer the result

1. The part of the central nervous system affected: If muscle-supplying parts of the CNS are infected, severe muscle atrophy can result. Horses seem much less able to recover from this kind of damage than damage to a part of the brain, for example.

2. Immune status: Each horse's immune system and ability to fight off EPM infection varies greatly.

3. The time that elapses between onset of clinical signs and beginning of treatment—the longer the lag before treatment, the poorer the clinical result.

4. The duration and type of treatment.

5. The strain of *S. neurona*: Some strains might be more virulent than others.

6. The infective dose (i.e., the number

EPM at a Glance: The Must-Know Facts

Potentially, any horse living in an area with a opossum population is at risk to develop equine protozoal myeloencephalitis (EPM). In general, EPM is not specific to a certain age, breed, gender, or discipline. However there are studies showing an increased incidence among racing (Thoroughbred and Standardbred) and western performance horses. This could be due to career-related stresses. Other risk factors include living in proximity to a wooded area; living on a farm where other horses have been diagnosed with EPM; and concurrent exposure to stressful events including travel, relocation, heavy training, or recent illness or injury.

There is no vaccine on the market to prevent EPM, so management practices must be implemented to reduce the risk of exposure, including:

- Protecting feed/water sources from opossums to avoid contamination with *S. neurona* sporocysts
- Reducing exposure to areas inhabited by opossums
- Reducing stress to avoid suppressing the immune system

The key to successful treatment and recovery is early detection and aggressive therapy. Veterinary involvement is essential to help rule out other neurologic diseases that can mimic EPM. Horses should be monitored closely for the signs of EPM, including:

- Incoordination
- Asymmetric muscle atrophy
- Weakness
- Head tilt, ear droop
- Difficulty swallowing
- Lameness
- Behavior change
- Unexplained decrease in performance

Therapy includes administration of an FDA-approved anti-protozoal product for a sufficient length of time. Protazil™, a pelleted formulation of diclazuril, is the newest FDA-approved EPM treatment.

For more information on EPM and Protazil™, including complete product information, visit Protazil.com or call 800.521.5767

By Dr. Wendy Vaala, senior equine technical services veterinarian for Merck Animal Health

of protozoal sporocysts the horse ingests). A big dose or series of moderate doses are more likely to cause rapid disease progression than a single moderate dose or series of small doses.

Signs of EPM can range from subtle and atypical lameness to seizures. MacKay said this variability is most likely due to the fact that "the organism can invade any part of the spinal cord or brain, causing from one to several foci of damage; thus, the signs can be brain signs (facial paralysis, head tilt, and staggering), weakness and incoordination in one to all limbs, or wasting of muscles anywhere in the body."

Like MacKay, Amy Johnson, lecturer in clinical studies at the University of Pennsylvania, believes some of this discrepancy between affected and exposed horses might be due to factors affecting the horse itself, particularly genetics.

"As we learn more about the genetics of immunity I think we will realize that certain horses' immune systems are 'programmed' to behave in ways that make them more susceptible to EPM, while others are relatively resilient to infection," she said.

The protozoa's journey in the horse is not yet entirely clear. One might expect, looking at the brain or spinal cord of an EPM-infected horse, to see legions of parasites. However, this is not the case.

According to Howe, while "parasites are there and will damage some cells because they live inside the cell and will rupture it, not many parasites are found in the CNS, but there is a very strong (local) immune response."

Howe suggests the inflammation resulting from the localized immune response causes more tissue damage than the parasites themselves.

This raises the question of the immune system's role in EPM development.

"In horses that come down with EPM, is it because they have too robust a response, causing damage to the CNS?" asked Howe. Or, do horses develop EPM because they are immune-suppressed and unable to clear the initial stages of the parasite from the body? Howe believes some horses develop EPM due to more than one factor.

Further, the parasite itself might influence the horse's ability to combat the disease. In a 2004 study published in the *Journal of Parasitology*, for instance, researchers noted EPM-infected horses had decreased immune responses to parasite-specific antigens (surface proteins on the organism) of *S. neurona*.

"There is definitely strain variation among *S. neurona*," noted Johnson. "What we don't know is exactly what this strain variation means. I suspect that different strains may have different degrees of virulence (ability to cause disease) but we are still in the early stages of working out how parasite strain affects the likelihood of CNS infection, the signs the horse may or may not show, and the susceptibility to different types of treatment."

Does My Horse Have EPM?

Diagnosing EPM in the live horse is far

from straightforward; veterinarians use tests designed to detect antibody to the various *S. neurona* antigens. MacKay stated that one of the common misconceptions he hears regarding EPM is that veterinarians can diagnose the disease reliably with a blood test.

"Unfortunately, this probably is not true," he said. "Negative blood tests have value but there are frequent false-positive blood tests. The best test currently available requires simultaneous spinal fluid and blood samples."

Because diagnosing the disease accurately has been so difficult, many owners and veterinarians base their diagnosis on whether the horse responds to EPM treatment after ruling out other causes of lameness or neurologic disease. MacKay called this approach "a defendable strategy based on the notion that instead of spending money on diagnostics you may as well spend it on treatment and just see what happens. This was especially true when diagnostics were quite unreliable."

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Protazil has been approved by the FDA as a treatment for EPM (see sidebar)

However, "This calculus may have changed with the advent of a very promising test that seems to have high sensitivity and specificity (ability to correctly identify an affected animal positive and an unaffected animal negative—reducing false positives and negatives) for EPM diagnosis," he added. "Also, in light of the fact that only about 60% of EPM horses respond to treatment, the other 40% would be wrongly considered EPM-negative using the treatment-response approach to diagnosis."

As MacKay noted, the test measures the *S. neurona* antibody concentration in both the bloodstream and the cerebrospinal fluid (CSF). Previously, scientists thought *S. neurona* antibodies found in the CSF indicated the protozoa's presence in the CNS and, therefore, represented a positive EPM status.

However, it turns out that antibodies to foreign proteins, such as certain *S. neurona* antigens, present in the blood can also be found in proportionate levels in the CSF, even in healthy horses.

S. neurona appears to produce several surface antigens, and it seems that not all strains of the parasite express these same antigens.

Given that no test can identify the presence of *S. neurona* organisms themselves in the CNS of the live horse, veterinary consensus seems to be that diagnosis requires a multifaceted approach including complete physical and neurologic exam, diagnostics such as radiographs (X-rays) to rule out other causes of clinical signs, and a careful interpretation of serum and CSF antibody levels.

Prevention and Treatment

"Unfortunately," said MacKay, "there is no vaccine (against EPM), and it is not practical for a horse to be on lifelong EPM treatment, so the only preventative strategy that we know of is to reduce exposure to *S. neurona* 'eggs' (sporocysts). The best way to prevent accidental ingestion (of these sporocysts) by horses is to keep opossums away from horse feed and water. Do not store hay for long periods of time (where they might become home to opossum nests); keep feed inside galvanized containers; and do not leave fruit (lying around) or pet or bird feed on the ground. Fence horses away from ponds, rivers, and the edge of woods (all prime opossum habitats). Be on the alert for any early signs and seek immediate veterinary attention."

Regarding the various drugs approved for treating EPM, MacKay said, "On the basis of multi-center studies, there is no evidence for better outcomes by any of the approved treatments available."

However, he explains each treatment has something different to offer:

1. The traditional EPM combination sulfadiazine/pyrimethamine (available as a compound from pharmacies) is relatively inexpensive, although it's associated with potential toxicity problems;
2. Ponazuril (Marquis) rarely presents toxicity problems and is marketed in a palatable, easy-to-administer paste;
3. Diclazuril (Protazil) is formulated as a pellet that can be top-dressed easily on a horse's regular feed. It also presents a very low risk of toxicity.

However, MacKay said, "On the basis of the rather low cure rates cited above, it is clear that the ideal EPM treatment has not been found yet."

In conclusion, MacKay said, "because there is no foolproof method of prevention, early diagnosis and treatment are the keys to a good outcome in a horse that shows the signs of EPM."

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