

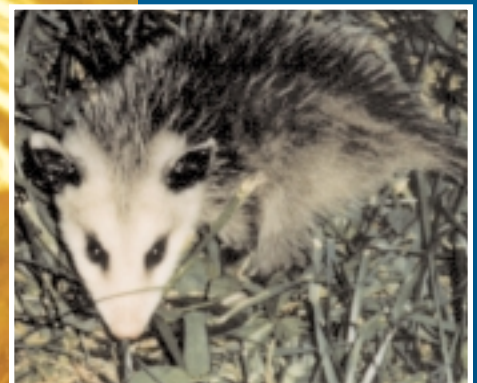
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# VETERINARY EXCHANGE®

SUPPLEMENT TO COMPENDIUM ON CONTINUING EDUCATION FOR THE PRACTICING VETERINARIAN®



**Diagnosing  
Equine Protozoal  
Myeloencephalitis**



VETERINARY

# EXCHANGE<sup>®</sup>

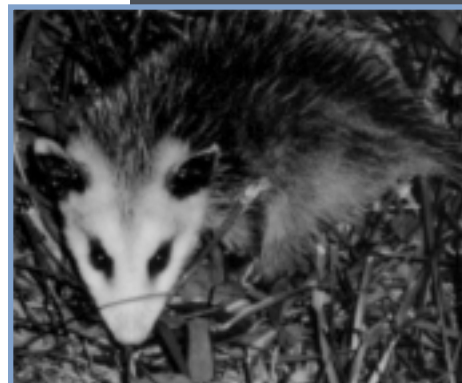
SUPPLEMENT TO COMPENDIUM ON CONTINUING EDUCATION FOR THE PRACTICING VETERINARIAN<sup>®</sup>

## Diagnosing Equine Protozoal Myeloencephalitis

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Supplement to Compendium on Continuing Education  
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This issue of *Veterinary Exchange*<sup>®</sup> on equine protozoal myeloencephalitis is the latest in a series of supplements that accompany *Compendium*. Each of these pieces focuses on a specific topic of interest to veterinary practitioners. While the material in *Compendium* is published only after intense peer review, *Veterinary Exchange*<sup>®</sup> provides an informal outlet for the dissemination of practical, experiential information written by and for veterinarians.

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Dr. Reed is Professor of Equine Internal Medicine at the College of Veterinary Medicine, Ohio State University, Columbus. His primary research interests include cervical vertebral stenotic myelopathy and its association with osteochondroses and other developmental orthopedic diseases as well as equine protozoal myeloencephalitis. He received his DVM from Ohio State University in 1976 and is the author of over 60 articles, book chapters, and abstracts. In 1987 Dr. Reed was the editor of the equine edition of *Veterinary Clinics of North America*. He is a diplomate of the American College of Veterinary Internal Medicine.

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**E**quine protozoal myeloencephalitis (EPM) is a serious and sometimes fatal neurologic disease of horses throughout the world. EPM is caused when protozoal parasites infect and invade a horse's central nervous system. This disease has been recognized in horses since the mid 1960s, but it was not until 1974 that the causative organism was described as a "Toxoplasma-like protozoan."<sup>1</sup> The organism was identified and named *Sarcocystis neurona* in 1991.<sup>2</sup> Another organism, *Neospora hughesi*, has been recently identified as a cause of EPM as well.<sup>3</sup> The life cycles of these organisms are still being investigated. It is thought that the opossum is the definitive host of *S. neurona* and horses become infected by ingesting feed or water contaminated with fecal matter from infected opossums. Horses with EPM may present with a variety of clinical signs. The disease may vary from acute to insidious onset of focal or multifocal signs of neurologic disease. The disease tends to have a progressive course; however, in some horses the disease appears to stabilize or remain static for a while.

## QUESTION: *Do all horses infected with Sarcocystis neurona develop clinical disease?*

**A**NDREWS: No! Like most infectious diseases, many horses are exposed to the agent, but few develop clinical disease. The estimated incidence and/or prevalence in the horse population is 0.5% to 10%, the latter being higher than expected. In seroprevalence studies, 25% to 60% of horses have serum antibodies against *S. neurona*,<sup>4</sup> but the percentage of horses with clinical neurologic disease is very low. There may be several reasons why every horse exposed to *S. neurona* does not develop clinical neurologic disease, including the number of parasites ingested by the horse, viability and virulence of the parasite, the immune status of the horse, previous exposure to the parasite, and the presence of concurrent diseases. We assume from the infection studies of *S. neurona* that infection follows the fecal-oral route. Organisms are ingested by the horse and they gain entrance into the vascular system by way of the gastrointestinal tract. The blood vascular system spreads the organism to the central nervous system (CNS) where the parasite infects gray and white matter, leading to focal or multifocal neurologic signs. The number of parasites that the horse ingests may be one reason that some horses do not develop clinical neurologic disease. The number of *S. neurona* oocysts necessary for infection is not known; some horses may ingest a small number, resulting in immunity but not infection.

The viability or virulence of the parasite is important in causing disease. There are likely to be several strains of *S. neurona* that cause equine protozoal myeloencephalitis (EPM). In a recent meeting that I attended, it was noted that *S. neurona* isolated in one laboratory would only grow in epithelial cells from skin, whereas the *S. neurona*

from another laboratory would only grow in bovine mononuclear cells. Thus these two organisms may be two different strains with different virulence and different abilities to cause disease in horses. Furthermore four species of *S. neurona* recently were isolated from opossum feces, which may be different organisms or different strains of *S. neurona*. Whether different strains or organisms, their ability to cause disease may be different. Highly virulent strains may be more able to invade and cause disease in the CNS.

The immune status of the horse may affect whether the horse gets clinically ill or not. If the animal is undergoing a stressful event, such as long-distance transport or overcrowding, or is being given exogenous glucocorticoids, immunosuppression may occur. A horse that is immunosuppressed may be more susceptible to the neurologic disease caused by *S. neurona*. However, recent information suggests that administering glucocorticoids to horses before exposure to *S. neurona* may reduce inflammation and lessens the neurologic signs associated with EPM.

Previous exposure to the parasite may determine if the horse will become clinically ill. Small doses of the parasite over time (chronic exposure) may lead to acquired immunity. Concurrent diseases may determine whether clinical illness is seen. Many viral diseases in the horse, such as equine herpes virus (EHV) and equine influenza, are immunosuppressive and may predispose horses to EPM if they are exposed to *S. neurona*.

**B**ERNARD: I agree that all horses infected with *S. neurona* do not develop clinical signs. We know that

exposure to *S. neurona* is very high, as indicated by the frequent identification of horses with positive antibody titers. A positive serum titer indicates exposure and subsequent antibody response to exposure. Only a small percentage of horses exposed will develop clinical signs. As with other organisms that cause disease, there are other factors involved in the manifestation of clinical signs. First, the organism must be virulent or capable of causing disease, and second, there are host factors, which are critical to the outcome of infection. The host defense mechanism must be overcome by the organism to result in clinical disease; therefore host immunity plays a critical role in the factors that result in clinical signs of EPM. In addition to immunity, the infective dose (number of organisms reaching the CNS) and the location of the lesions may also influence the outcome of exposure.

**FURR:** Although there is no empiric data to confirm this, my personal belief is that all horses infected with *S. neurona* do not develop clinical signs. The widespread and high seroprevalence to *S. neurona* coupled with the relatively small proportion of animals that truly demonstrate clinical signs suggest that animals may carry the infection without demonstrating clinical disease. In addition, reports of exported horses developing the disease long after export suggests a long prodromal phase of the disease is possible. A final consideration is that a similar organism that affects humans (*Toxoplasma gondii*) can be carried in the CNS for many years without evidence of clinical illness.

**MACKAY:** If one accepts that a positive serum Western blot indicates recent or current infection with *S. neurona*, then less than 1% of infected horses show clinical signs of EPM. There are probably at least four general factors that determine whether inapparent infection progresses to EPM. (1) *Dose:* Experiments with other *Sarcocystis* species (e.g., *S. tenella* in sheep and *S. cruzi* in cattle) have shown that there is a close relationship between challenge dose and clinical result. For most of these organisms, it is possible to establish LD<sub>50</sub> values, which may range from 50,000 sporocysts (*S. capracanis* in goats) to  $2 \times 10^6$  sporocysts (*S. arieticanis* in sheep). Although it is clear from experimental infection studies<sup>5</sup> in horses that have used up to  $3 \times 10^7$  sporocysts without causing severe clinical signs that *S. neurona* is of relatively low pathogenicity, it is logical to assume that some form of a dose-response relationship exists. Whether sporocysts are ingested as a single bolus (as in experimental settings) or as small aliquots over an extended period is an unresolved issue. (2) *Immune status:* It has been well documented that prior subclinical infection with *S. cruzi* in calves protects against subsequent massive homologous (*S. cruzi*) challenge, though the dura-

tion of this immunity is uncertain. Therefore it is likely that *S. neurona*-naïve horses (usually young animals) are more susceptible to serious infection and EPM than are horses that have been or are subclinically infected with the organism. In a more general sense, impairment of the immune system is widely believed to contribute to progression of infection with *S. neurona* to EPM. Such stressors as pregnancy, lactation, transportation, exhaustion, and intercurrent disease are thought to be risk factors for EPM that act via impairment of immune function. However, it is unlikely that simple broad immunosuppression accounts for most cases of EPM. Recently conducted studies have shown that dexamethasone did not increase the severity of neurologic signs in *S. neurona*-challenged horses.<sup>6</sup> Instead, more subtle interactions between *S. neurona* and immune responses are likely. In the case of other sarcocystid protozoa, such as *T. gondii* and *Neospora caninum*, competent Th-1 responses mediated by such cytokines as interferon  $\gamma$  and interleukin 12 are important in resistance to overwhelming infection. This is also likely to be the case with EPM. (3) *Genetics:* Relative resistance to sarcocystid infections usually is at least partially heritable. In part, this may be associated with a genetic predisposition toward Th-1 responses (protective) versus Th-2 responses (permissive). (4) *Virulence of the organism:* Although there are no data on the subject (limited analyses of isolates thus far have not revealed major differences), it seems likely that there are different strains of *S. neurona*—some may be more invasive or neurotropic than others. In summary, horses are easily infected by *S. neurona* but are quite resistant to the development of EPM. Factors that may increase the risk of EPM include the dose and virulence of the infecting strain and the genetic makeup and immune status of the horse.

**REED:** I also do not believe that all horses infected with *S. neurona* develop clinical disease. The most immediate rationale for this is that in such areas as Ohio and surrounding states, greater than 50% of horses have antibodies in their serum, indicating these animals have been exposed to the organism.<sup>7</sup> Still, the number of horses demonstrating clinical signs of disease is much lower than this. It is possible that many horses are exposed to the organism but never develop clinical infection because natural defenses of horses are capable of fighting the infection or preventing the organism from entering the CNS. It is also possible that even if the organism enters the CNS, normal defense mechanisms of horses' neurologic system might combat the organism and clear it from the system. In horses that have been experimentally infected with *S. neurona*, it is not easy to reisolate the organism from tissues harvested at necropsy, and many of the horses that are infected develop clinical signs that often appear to lessen over time despite no treatment.

**SUMMARY:** Not all horses infected with *S. neurona* develop clinical disease. The percentage of horses with clinical disease is very low, though 25% to 60% of horses in seroprevalence studies have serum antibodies against *S. neurona*. The reasons for this may include the

number of parasites ingested by the horse, viability and virulence of the parasite, the immune status of the horse, previous exposure to the parasite, and genetics. It is also possible that in some cases there may be a long prodromal phase before clinical disease is seen.

## QUESTION: *What are the geographic or seasonal variations, if any, in the incidence of EPM?*

**BERNARD:** The geographic distribution of EPM coincides with distribution of the definitive host: the opossum. The American opossum is found in South, Central, and North America. In the United States, the distribution of the disease varies with the distribution of the opossum; horses are less likely to be affected in areas where opossums are scarce. A seasonality to the disease has not been noted. It would make sense that the disease would be more prevalent where the opossum is more active; however, the prepatent period (time from infection to disease) has not been determined and may be quite variable.

**ANDREWS:** In the early literature, many investigators thought that EPM was only present east of the Mississippi River. But clearly, from published seroprevalence studies, serum antibodies to *S. neurona* have been found in 10% to 40% of horses in Oregon and Utah.<sup>4,8</sup> Furthermore, the disease has now been reported in most areas in the Western Hemisphere, including the United States, Canada (including the Maritime Islands), Mexico, Panama, and Brazil. The disease has been reported in Great Britain and Europe in horses imported from the Western Hemisphere but has not been reported in horses native to those countries.

There appears to be a decreased seroprevalence in horses in the Rocky Mountain states. A recent study of wild mustangs in Utah showed that less than 10% had serum *S. neurona* antibodies.<sup>4</sup> This difference in seroprevalence is probably caused by the absence or presence of the definitive and/or intermediate hosts for the parasite and the environmental conditions in those areas. One of the known definitive hosts for EPM is the opossum. Disease prevalence may be associated with range of this animal. However, recent EPM studies in Utah and Prince Edward Island, outside the opossum habitat, showed seroprevalence rates of 10% and 30%, respectively.<sup>4</sup> Other species or contaminated feed sources clearly are responsible for transmission of EPM.

Seasonal variations seem to be important in the prevalence of EPM in horses. Seroprevalence studies by Saville et al and the group at The Ohio State University<sup>7</sup> have shown that exposure to *S. neurona* is related to the number of freezing days that occur in an area. In that study, horses in northern Ohio, along Lake Erie, had less exposure to *S. neurona* than horses in southern Ohio, along the Ohio River. Thus oocysts of *S. neurona* may be more susceptible to freezing and may overwinter better in warmer climates, leading to greater exposure and possibly a greater prevalence of clinical disease.

**FURR:** In my area we see lots of horses with EPM, and the peak incidence is in the spring and summer months, though new cases are seen throughout the year. I believe that more cases are seen in summer because that is when most owners are actively using their horses and the more subtle gait abnormalities can be detected, leading the owners to seek veterinary advice. The chronicity of EPM makes it difficult to determine when infections occur, and seasonal variations in incidence are masked. Geographic variations in disease have not been systematically studied, but exposure to the parasite, reflected as seropositivity, is more readily determined. Research has shown different seropositive rates in different regions of Ohio and Oregon.<sup>7,8</sup> In Ohio, decreased exposure was noted in regions with more days below freezing. In Oregon, less exposure was noted in the eastern region of the state (65% positive versus 22%). The authors of the study indicated that the eastern region of the state has fewer opossums than the western region. In addition, the western region of Oregon has higher rainfall and lower summer temperatures than the eastern region. These findings suggest that environmental conditions and the presence of vectors have a significant role in the incidence of exposure and presumably disease. Therefore, local factors may play a role in transmission of the disease. From a clinical perspective I certainly see farms that have a high-

er incidence than others in the same locale, but it should be recognized that many confounding factors may play a role in this and it is difficult to make any firm conclusions at this time.

**MACKAY:** EPM tends to occur in warm and temperate areas of the Americas that have reasonable rainfall. Conversely, very cold (e.g., Canada) or dry (e.g., Utah) regions have very low prevalence of EPM. It is thought that these trends reflect climatic effects on host animals and/or sporocysts. Blythe et al<sup>8</sup> showed decreasing prevalence of *S. neurona* infection (as indicated by positive serum Western blots) among horses in progressively more arid regions of Oregon. Saville et al<sup>7</sup> found that seroprevalence decreased proportionally as the number of freezing days increased in the northern parts of Ohio. Resident horses in islands off the American mainland that lack resident opossums (e.g., Puerto Rico and Prince Edward Island) generally have minimal or no EPM. Microclimate also may have an effect on disease prevalence. Saville<sup>9</sup> showed that risk of EPM was 50% lower when a creek or river was present on a farm. The interpretation of this observation was that opossums were likely to drink from the river instead of horse waterers. Conversely, disease risk doubled when woods were present, presumably because woods provided habitat for hosts of *S. neurona*. Saville also found that new cases of EPM were lowest in winter and increased as ambient temperature increased. The risk in summer was sixfold higher than that in winter.

Numerous confounding factors related to the seasonal movement and training of horses also may have contributed to these results. Additional information regarding geographic and seasonal variations will be published later this year when the National Animal Health Monitoring Survey (NAHMS) releases the results of its 1998 survey of EPM in the US.

## QUESTION: *What clinical signs or historical findings, if any, lead you to consider EPM?*

**FURR:** The hallmarks of EPM are asymmetric ataxia or multifocal neurologic disease. Owners will often present these horses because of observed stumbling or weakness. These signs are usually worse when the horse is ridden downhill or asked to perform complex maneuvers (e.g., lead changes, collection, etc.). In addition, although acute disease can occur, chronicity is usually present. Given the high incidence of orthopedic disease

**REED:** The geographic distribution of horses affected by EPM does appear to follow a pattern similar to the location of opossums. In addition, there is a seasonal variation. In the recent study conducted by Dr. Saville at The Ohio State University, horses diagnosed with EPM were compared with two groups of horses presented to the veterinary teaching hospital: one was a group of horses presented for neurologic diseases other than EPM, and the other was a group of horses presented for problems not related to the CNS. In this study, a seasonal effect for the development of EPM was noted: There was a higher incidence of EPM in spring, summer, and fall than in winter. Horses on farms where previous cases of EPM had been diagnosed were also at a higher risk for developing EPM. In Ohio, horses located in parts of the state that had the highest number of freezing days had a lower incidence of seropositive rates despite having similar numbers of horses at risk in these areas.

**SUMMARY:** The geographic distribution of EPM coincides with distribution of the definitive host: the opossum, which is found in South, Central, and North America. Other species or contaminated feed sources may be responsible for transmission of EPM. One study showed that rates of EPM are lower when a creek or river was present on a farm, perhaps because opossums were likely to drink from the creek or river instead of horse waterers.

Studies have shown that exposure to *S. neurona* is related to the number of freezing days that occur in an area. Also, one study showed a higher incidence of EPM in spring, summer, and fall than in winter. Some of the seasonal variations of diagnosis may be related to when horses are actively training and subtle changes in gait are more likely to be noticed and evaluated.

(lameness) mimicking neurologic abnormalities, failure to respond to phenylbutazone or other antiinflammatory drugs often suggests a neurologic, rather than orthopedic, cause of the stumbling.

**MACKAY:** The classic signs of EPM—including rapid muscle atrophy at a discrete location, asym-

metric gait abnormalities, or any combination of signs that suggest multifocal lesions—obviously immediately raise suspicion of the disease. Examples might include atrophy of one side of the tongue and severe weakness in the opposite pelvic limb or weakness and muscle atrophy in one thoracic limb and weakness and ataxia of the opposite pelvic limb. A sudden onset of signs is also classic. Any combination of signs attributable to brain disease *not* accompanied by fever (e.g., sudden onset depression with head tilt and facial paralysis on one side) is also highly suggestive of EPM. Although the foregoing presentations are quite easily interpreted when found, they represent only a small proportion of all cases of EPM.

Perhaps the most common sign is subtle, hard-to-diagnose, insidious-onset pelvic-limb lameness. Riders may notice that the rear end of the horse seems unstable particularly around turns. Drivers of Standardbreds may notice that the horse leans on the outside shaft around turns. Thoroughbreds may “cross canter” or otherwise interfere at the gallop. Trotters are more prone to “break” early in a training session or race. When a conventional lameness examination is done, the site is difficult or impossible to localize, even with joint blocks, though vague signs of back and/or gluteal pain often are noticed. Such horses often are treated empirically with intraarticular medications, internal blisters, and the like. Careful neurologic examination often reveals signs that are quite indicative of neurologic disease, including poor resistance to lateral pulling of the tail while the horse is walking, swinging out of a pelvic limb (circumduction) while the horse is walking in small circles, pivoting around a pelvic limb when the horse is pulled laterally in very tight circles, stiffness or excessive flexion of a limb or limbs during walking, dragging of the toes of a limb or limbs, or interference between sets of limbs (usually between the hooves of the thoracic limbs). In pleasure, endurance, or show horses, the first sign often is increased frequency of stumbling or clumsiness. This may be particularly obvious in horses performing such precision skills as dressage or show jumping.

In all cases, the suspicion of EPM increases when there is not another reasonable explanation for the signs: In other words, the lameness cannot be explained by musculoskeletal disease or by any other common neurologic disease (particularly cervical stenotic myelopathy or “wobbles”). Finally, it must be said that almost any neurologic sign—including rare presentations, such as seizures or paralysis of the caudal structures (including the tail, anus, and bladder)—is possible with EPM. In these rare cases, other differentials probably would be more highly considered than EPM.

**A**NDREWS: EPM should be considered whenever a horse with neurologic disease is presented because

it can have many clinical signs depending on where it localizes in the nervous system. EPM is usually considered the top differential when horses present with insidious onset lameness that cannot be localized in one or more limbs. EPM is usually classified by the owner or RDVM as a “high lameness” (above the carpus or tarsus) that cannot be blocked out by local anesthetic agents. Horses with EPM usually have undergone several surgical procedures, such as a medial patellar desmotomy or lateral digital extensor tenotomy.

Horses that are suspected of having EPM usually have asymmetrical gait deficits of neurologic origin, including weakness (knuckling, stumbling, dragging the toe, and dipping of the trunk on weight bearing), spasticity (stiff, stilted gait with lack of joint flexion), and ataxia (increased truncal sway, crossing the limb under the body while walking, circumduction of the limb away from the body, waving the limb in the air while walking, and searching for the ground with the limb before placement). A small percentage of horses may have muscle atrophy, a decreased piniculus reflex along the body, and unilateral weak anal sphincter tone. Older horses usually have a history of good performance followed by a decline in performance; for example, a racing time that decreases over several months or follows the onset of clinical disease.

Acute cases of EPM are quite severe. The following signs are usually acute manifestations (1- to 2-day onset): neurologic signs of head tilt, drooping of the ears, nystagmus, and ptosis of one or both eyes. Behavioral changes—including somnolence, dementia, and aimless wandering—may occur if the brain stem is involved. Horses may rarely present with seizures if lesions occur in the cerebrum.

**R**EED: Evidence of any neurologic problems should trigger suspicion of EPM. However, asymmetric neurologic gait deficits with muscle atrophy should be considered the most likely indicators of multifocal disease and EPM. The history often indicates that other horses on the premises have been affected by neurologic disease. The onset is usually a gradual progression of signs, though in some cases the disease can have a rapid onset and a rapidly progressive course. Such head signs as seizures and cranial nerve deficits are also typical of EPM.

**B**ERNARD: EPM may affect any area of the CNS of the horse; therefore the disease can result in a wide variety of neurologic signs. Clinical signs of EPM are primarily ataxia and weakness as a result of spinal cord dysfunctions. Horses will exhibit various forms of spinal ataxia involving the pelvic and/or thoracic limbs. Muscle atrophy may be seen if gray matter

of the spinal cord is involved. Lesions of the brain stem can cause a variety of cranial nerve deficits, including difficulty in swallowing, head tilts, or facial nerve deficits.

**SUMMARY:** The classic signs of EPM include rapid muscle atrophy at a discrete location, asym-

## QUESTION: *When you suspect EPM, what other diseases should be ruled out?*

**ANDREWS:** When acute neurologic disease occurs, rabies should always be ruled out first because of its zoonotic potential. Other diseases that should be ruled out in acute cases include the viral encephalitides (eastern equine encephalomyelitis [EEE], western equine encephalomyelitis [WEE], Venezuelan equine encephalomyelitis [VEE; regional], West Nile virus [regional], and equine herpesvirus 1 [EHV1]). The viral encephalitides usually are associated with unvaccinated animals that are exposed during the mosquito season, whereas EHV1 usually is associated with respiratory disease outbreaks on farms and horses that have had abortions. In the young horse, congenital malformations of the cervical vertebrae (cervical stenotic myelopathy, atlanto-occipital malformations [Arabian]) must be ruled out first. In horses with more insidious onset of clinical signs, lameness must be ruled out first and foremost. Subtle hock lameness or foot problems can look like EPM but can be ruled out quickly with proper physical and lameness examinations. Other diseases that occur less frequently but must be ruled out include polyneuritis equi, aberrant parasite migration (*Hali-cephalobus deletrix*), equine degenerative myelitis, and equine motoneuron disease.

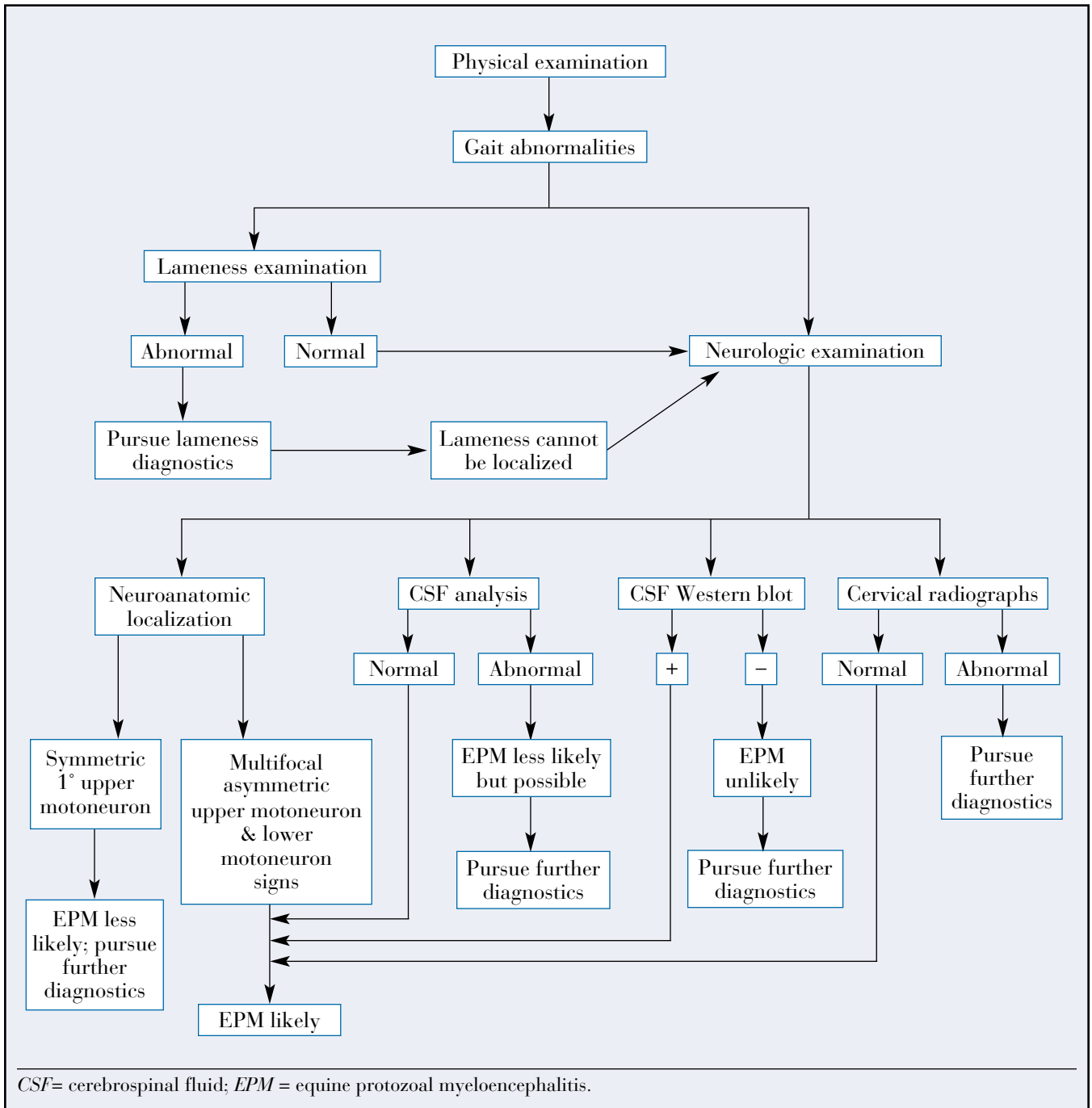
**MACKAY:** When a horse has signs attributable to spinal cord disease, possible differential diagnoses include cerebrospinal meningitis, equine degenerative myeloencephalopathy, trauma with or without vertebral fracture, EHV1 myeloencephalopathy, extradural neoplasia (usually lymphosarcoma), migrating metazoan parasite (e.g., large strongyle), epidural abscess, septic or degenerative intervertebral disk disease, spinal cord neoplasia, neuritis of the cauda equina, equine motor neuron disease, neuroborreliosis, and rabies. Common musculoskeletal diseases also must be considered. For horses with signs of brain stem disease (usually asymmetric

metric gait abnormalities, or any combination of signs that suggest multifocal lesions. Any combination of signs attributable to brain disease *not* accompanied by fever is also highly suggestive of EPM. Perhaps the most common sign is subtle, hard-to-diagnose, insidious-onset pelvic-limb lameness. In many horses the first sign often is increased stumbling or clumsiness. It is important to note that almost any neurologic sign is possible with EPM.

facial paralysis and head tilt with depression, but may include other signs), other conditions to be ruled out include temporohyoid osteoarthropathy with or without temporal bone fracture or active otitis media/interna, poll trauma with or without skull fracture, viral encephalitis, migrating parasite (including *Hali-cephalobus deletrix*), polyneuritis equi, extradural or basilar abscess, or neoplasia. For horses with signs primarily suggestive of forebrain disease, differential considerations include leucoencephalomalacia, frontal trauma, viral encephalitis, hepatoencephalopathy, neoplasia, cholesterol granuloma of the choroid plexus of the lateral ventricle, equine infectious anemia, infarct, renal encephalopathy, metabolic derangement (e.g., hyponatremia), primary hyperammonemia, or juvenile or idiopathic epilepsy.

**REED:** When EPM is suspected, the primary rule outs are dependent on the neuroanatomic localization of the signs; for example, a horse with head tilt and nystagmus might have head trauma, such as damage to the base of the skull, or may have osteomyelitis of the stylohyoid bone. However, a horse with signs of spinal ataxia could have cervical vertebral stenotic myelopathy or equine degenerative myelopathy or trauma.

**BERNARD:** Because of the difficulty in definitively diagnosing EPM, extensive efforts must be made to rule out other neurologic diseases. EPM can infect any area of the CNS; therefore the clinical signs of the disease can mimic other neurologic conditions of the horse. If spinal ataxia/weakness is present, cervical compressive myelopathy should be considered a primary differential. Equine herpes myeloencephalopathy, equine degenerative myelopathy, and traumatic injury should be considered. If the cerebrum or brain stem is involved, the



*Diagnosing equine protozoal myeloencephalitis.*

numerous diseases that can affect these anatomic locations should be considered and ruled out.

**FURR:** Both neurologic and nonneurologic causes of lameness should be ruled out. The most common to consider include orthopedic disease, cervical compression (equine wobbles), EHV1 myeloencephalopathy, cervical arthritis, and equine degenerative myeloencephalopathy.

**SUMMARY:** When EPM is suspected many common and uncommon diseases should be ruled out. Both neurologic and nonneurologic causes of lameness should be ruled out. In the young horse, congenital malformations of the cervical vertebrae (cervical stenotic myelopathy, atlanto-occipital malformations [Arabian]) must be ruled out first. In horses with more insidious onset of clinical signs, lameness must be ruled out first. Also, the primary rule outs are dependent on the neuroanatomic localization of the signs.

# QUESTION: *Describe the diagnostic steps you take when you suspect a horse has EPM.*

**REED:** The first important step is to obtain an accurate history that includes clinical signs, duration, previous treatments and response, as well as whether other horses have been affected on this premise. The next and most important step is a careful neurologic examination to rule out lameness or other musculoskeletal disease. This should be followed by appropriate radiographs of the skull, cervical vertebrae, or, rarely, other vertebral locations. They should be accompanied by collection of CSF from either the atlanto-occipital or lumbosacral space and performance of Western blot testing of the CSF and serum for antibodies against *S. neurona* and *Neospora hughesi*. In some horses, additional testing, such as myelography or electromyography, may be helpful.

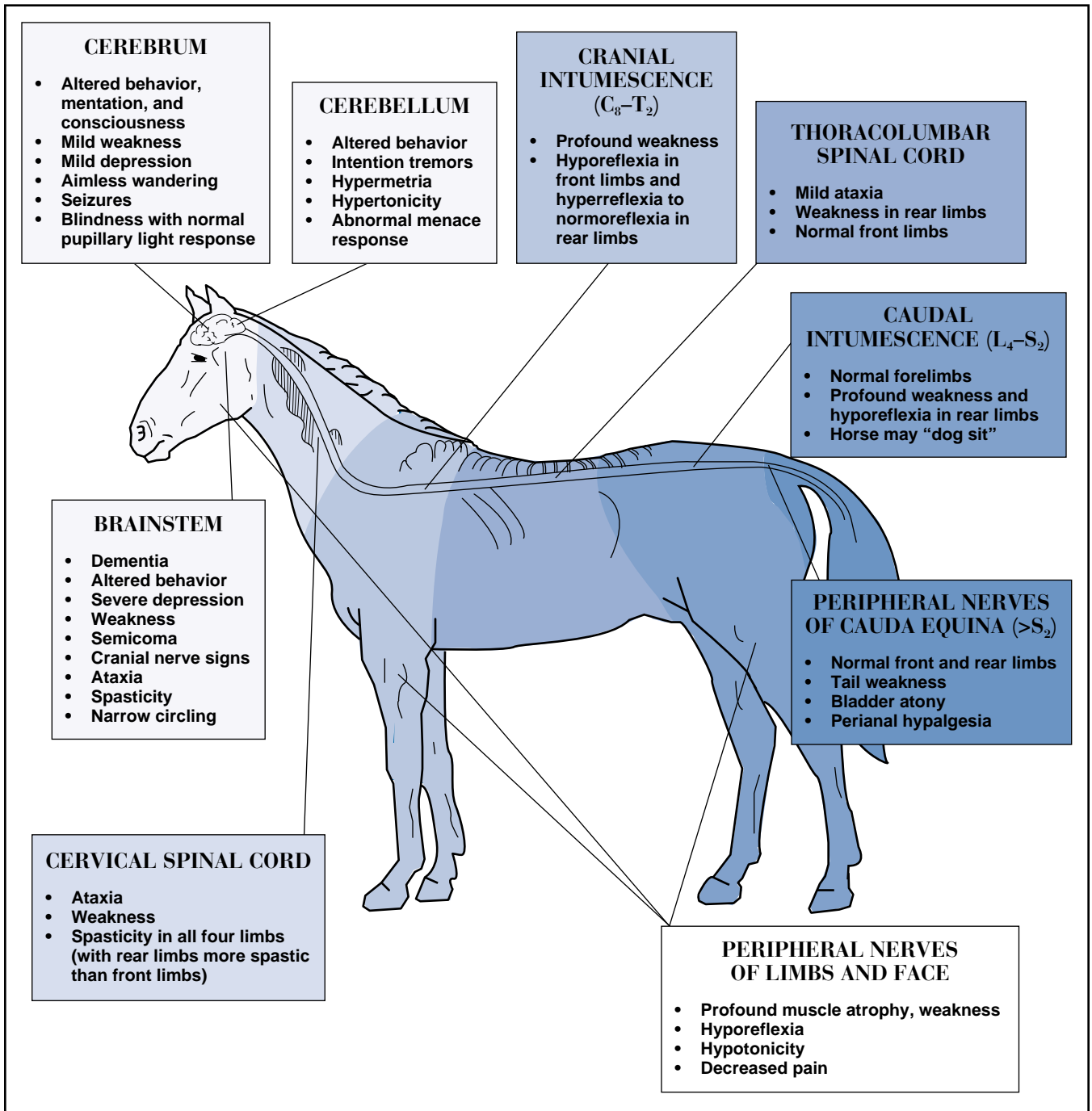
**MACKAY:** My diagnostic steps are (1) careful neurologic examination, possibly supplemented with lameness examination. (2) If spinal cord disease is suspected on the basis of the neurologic examination, and especially if the signs are consistent with cervical spinal cord disease, I will take standing plain cervical radiographs to help rule out cervical stenotic myeloencephalopathy. (3) If brain stem disease is suspected, I will take standing plain skull radiographs (including a dorsoventral projection) in an attempt to exclude temporohyoid osteoarthropathy or skull trauma. (4) If fore-brain disease is suspected, I will submit serum for hemagglutination inhibition titers against the common alphaviral encephalomyelitides. Very specific other diagnoses may be ruled in or out by other tests (e.g., blood ammonia concentration for hepatoencephalopathy). (5) I usually recommend that a CSF tap be performed and the fluid be submitted for routine cytology and for Western blot for IgG against *S. neurona*. I usually do not ask for albumin quotient and IgG index because I believe these tests lack sensitivity as measures of CSF contamination with plasma proteins or intrathecal production of antibody, respectively. However, I do recommend quantification of anti-17-kDa antibody (reported as “relative CSF quantity” by one of the commercial laboratories). I have found this value to be high only in convincing cases of EPM and in horses with experimental infections. It also can be used as a guide to treatment duration. (6) Many clients prefer to go through the initial steps outlined in 1 through 4 above and then begin treatment for EPM.

They use response to treatment over the next several weeks as a method of retrospective diagnosis. This is a perfectly reasonable method of supporting the diagnosis, and I recommend it myself when finances are a problem—2 months of therapy often costs less than a CSF tap and analysis. (7) A final possibility is to submit a serum sample for Western blot analysis (without an accompanying CSF sample). A positive result has little diagnostic value; however, a negative result has quite high negative predictive value for EPM (purported to be about 90%).

**ANDREWS:** First of all, owners of horses presenting to our hospital are thoroughly questioned about the history of the complaint, and horses undergo a complete physical examination. If gait deficits are part of the history, or physical examination reveals abnormal muscle symmetry or abnormal hoof wear, the horse has a complete lameness evaluation. If the horse is found to have lameness, the condition is thoroughly explored. If neurologic gait deficits are discovered, a full neurologic examination is done, including an examination of the cranial nerves and observation of the horse at a walk and trot in a straight line and in a circle. The horse is also walked up and down an incline to look for subtle abnormalities.

If the gait deficits are subtler, the owner is asked to work the horse under tack in a straight line or in a circle. Once the neurologic gait deficits are localized to either a focal or multifocal or diffuse region of the nervous system, a more intense examination of those areas is performed. In most all horses with gait deficits in all four limbs, cervical radiographs are taken and the minimum sagittal ratio is calculated per Moore et al.<sup>10</sup> If abnormalities are discovered, further diagnostics are pursued, including a bone scan of the cervical spine and usually all four limbs and back. Also, if indicated (minimum sagittal ratio of <0.5 at C2–7), a myelogram is performed to rule out a compressive spinal cord disease, such as cervical stenotic myelopathy.

If the signs are multifocal or focal and the cervical radiographs do not show arthritic changes or narrowing, a spinal tap is done and aliquots are sent to the laboratory to evaluate cytology (color, clarity, total protein, white blood cell [WBC] count, and red blood cell [RBC] count) and Western blot for EPM. Also, if indicated by history, physical, and neurologic examination, blood and paired CSF titers (taken 2 weeks apart) are sent to the state



*Clinical signs of EPM associated with regions of the nervous system.*

diagnostic laboratory to test for EHV1, EEE, WEE, VEE, and West Nile virus. With our current knowledge of the disease, a positive CSF Western blot test for *S. neurona* antibodies means active disease, so those horses are treated. If the Western blot comes back negative, other diagnoses are pursued.

**BERNARD:** The diagnostic steps when EPM is suspected include a complete physical and neurologic examination, serum and CSF testing, and when indi-

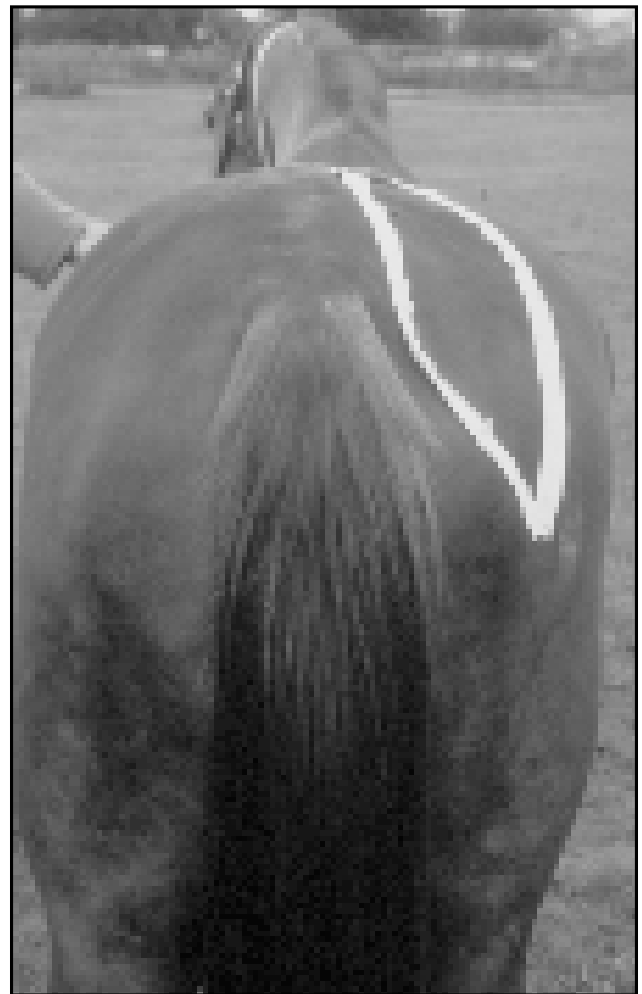
cated, other diagnostic testing necessary to diagnose or rule out other neurologic diseases. Other diagnostic tests include radiography of the head and vertebrae, myelography, nuclear scintigraphy, serology, and ancillary diagnostic tests. CSF is evaluated for antibodies to *S. neurona*, protein content, WBC count, and other indices.

**FURR:** When I am asked to examine a horse suspected of having EPM, I proceed with the physical and neurologic examination first and do the specific tests for

EPM last. Other, more common disorders should be ruled out first. In my experience, occult lameness is often present; therefore I will do a lameness evaluation first. In my experience, bilateral front feet lameness (from any cause) and bilateral hock lameness can lead to very confusing and erratic gaits that can mimic those of neurologic claudication. Hence, the evaluation should include jogging the horse in a circle to exacerbate front limb lameness. The examiner also should perform flexion of both hocks. If lameness is suspected, the area can be blocked using diagnostic nerve blocks, and the lameness examination can be repeated. If the lameness is blocked out, orthopedic disease should be considered the primary cause and pursued before evaluation of neurologic disease, unless there is compelling evidence of concomitant neurologic abnormalities.

Once the examiner is convinced that neurologic disease is present, such diseases as cervical compressive myelopathy, EHV1 myeloencephalopathy, and equine degenerative encephalopathy (EDEM) should be considered. A high index of suspicion should be maintained for cervical compression when examining young Thoroughbred or Standardbred horses with symmetric hind limb gait deficits. The clinical signs (e.g., symmetric weakness and loss of tail and anal tone) and history should be suggestive of EHV1 myeloencephalopathy, which can be supported by the findings of a spinal tap. EDEM causes symmetric abnormalities and is usually seen in younger horses. Therefore I consider a minimum database for evaluation of horses with EPM to be a lameness and neurologic examination, cervical radiographs, complete CSF evaluation (including Western blot), and blood Vitamin E concentration.

**SUMMARY:** When EPM is suspected the diagnostic steps include a complete physical and neurologic examination, serum and CSF testing, and other diagnostic testing necessary to diagnose or rule out other neurologic diseases. Other diagnostic tests include radiography



*Muscle atrophy associated with EPM.*

of the head and vertebrae, myelography, nuclear scintigraphy, serology, and ancillary diagnostic tests. CSF is evaluated for antibodies to *S. neurona*, protein content, WBC count, and other indices.

## QUESTION: *How do you interpret CSF results when you suspect EPM?*

**ANDREWS:** It is important to interpret the CSF results in light of the examination of the whole horse. Because horses can have a positive CSF Western blot test for *S. neurona* but not have active disease, it is

important for making an accurate diagnosis. I believe that CSF analysis should be used as a confirmatory test for EPM in a horse that is well worked up, rather than relying on it to be the sole test to make the diagnosis. It

can be difficult to interpret CSF from horses with neurologic disease because CSF parameters often can be normal even in severe neurologic disease.

I interpret CSF results in horses that I suspect have EPM by evaluating the Western blot test results in addition to the CSF cytology (color, clarity, total protein concentration, WBC counts, RBC counts), albumin quotient results, IgG index determinations, and CSF titers (rising paired titers). The Western blot is currently the best test for diagnosing EPM in horses. Its reported sensitivity and specificity is approximately 90%. The test is subject to the interpretation of the person or persons performing it and must be interpreted in light of the clinician's clinical and neurologic evaluation of the patient and the presence of blood contamination during CSF collection. A positive CSF Western blot test in a normal horse is not reliable in predicting active disease. The pretest probability of disease in a normal horse in the population is less than 30%; in other words, the probability of a normal horse in the population having active EPM that has a positive CSF Western blot test for *S. neurona* is approximately 29%. Whereas a positive CSF Western blot test in a horse with neurologic disease is much more reliable and has a pretest probability of nearly 90%. However, the negative predictive value in normal horses and horses with neurologic disease is greater than 90%. So a negative Western blot test is significant.

Before submitting the CSF sample for Western blot testing, I examine the sample for gross evidence of blood contamination. The first aliquot of spinal fluid that fills the syringe usually is contaminated with a small amount of blood. I save that aliquot for culture in case the cytology reveals suppurative or nonsuppurative meningitis. I usually collect the next two or three aliquots for various analyses. If the blood persists in the sample, I consider the sample contaminated but I do not discard the sample because it may still be helpful in ruling out disease (I will explain later). If the CSF sample has no evidence of gross blood contamination, I evaluate the CSF cytologic examination for evidence of blood contamination. If the CSF cytology shows an increased number of RBCs (>500 cells/ $\mu$ l), I consider the sample to be contaminated but I do not discard it. If the RBC count is <500 cells/ $\mu$ l, I consider the CSF sample acceptable and submit it with a serum sample for Western blot analysis for *S. neurona* antibodies. I also have the laboratory perform the CSF index determination (i.e., albumin quotient [ $\{\text{CSF albumin/serum albumin}\} \times 100$ ], which is an indicator of blood-brain barrier permeability or blood contamination of CSF, and IgG index [ $\{\text{CSF IgG/serum IgG}\}/\text{albumin quotient}$ ], which is an indicator of intrathecal production of IgG).<sup>11</sup> If the CSF Western blot test is positive (weak or otherwise) and the albumin quotient is less than 2.2, I interpret that as active disease. If the CSF Western blot test is positive and the albumin quotient is greater than 2.2, I interpret that as a false positive caused by blood contamination or damage to the blood-brain barrier. The

latter can occur with bacterial meningitis and/or EHV1 myeloencephalitis. The IgG index has been shown to increase with CSF blood contamination but is not reliable for predicting EPM infections. However, it may be helpful in determining response to therapy. If the CSF Western blot test is negative and the horse has acute or peracute disease, I interpret these results as a false negative and I recommend treatment for 30 days and a repeat spinal tap in 2 weeks. The antibodies to *S. neurona* may not have had adequate time to increase in acute or peracute infections.

I currently only submit samples for polymerase chain reaction (PCR) evaluation in horses that present with peracute or acute neurologic disease because in my opinion this test has a very low diagnostic value (poor specificity) and does not warrant the expense to the client. Also, in horses with peracute or acute neurologic signs of less than 10 days, I make every attempt to rule out rabies. I submit a sample of CSF for rabies titer and epilate several muzzle hairs for immunofluorescent antibody testing. I submit the blood-contaminated CSF sample along with a serum sample taken from that horse. The rationale for this is as follows: If the CSF sample is negative, there is a high probability that the horse does not have EPM (approximately 98% probability). If the CSF sample is positive and the blood sample is negative, there is a high likelihood that the horse has active disease—perhaps reactivation of a latent infection. If the CSF sample is a strong positive and the blood is a weak positive, I consider this indicative of active disease. If the CSF sample is positive and the blood is positive, an accurate interpretation cannot be made, and I recommend that the horse have a repeat spinal tap in 1 to 2 weeks.

**FURR:** I believe that it is important to run a complete analysis—not just the Western blot—when evaluating CSF test results for EPM. This provides the opportunity to consider and potentially rule out EHV1, meningitis, neoplasia, or trauma—conditions that I have found with the aid of the CSF analysis when evaluating horses for EPM. In addition, determining the RBC count is important in evaluating whether there is peripheral blood contamination. If the serum Western blot is strongly positive, even a few RBCs (10 to 20) in the sample can signal enough peripheral contamination to cause the sample to become falsely positive, though it will likely be a weak positive. It is important to recognize that this level of blood contamination will not cause visible changes in the CSF; therefore a laboratory cell count is essential. These weak positive cases should be interpreted with caution: The clinical signs should be compelling, and all other possible causes of ataxia should be eliminated before such a patient is diagnosed as having EPM. In other patients in which the spinal tap is uncontaminated with peripheral blood and is moderately or strongly posi-

tive and other causes of ataxia have been eliminated, I feel that the diagnosis of EPM is fairly solid.

**BERNARD:** Interpretation of CSF is primarily done by evaluation of antibody response to *S. neurona*. The presence of antibodies to *S. neurona* in CSF suggests the possibility of the presence of infection. There are several other possible explanations for the presence of *S. neurona* antibodies in CSF; therefore the antibody test is not definitive for EPM. Other testing that can be performed includes protein determination, RBC and WBC counts, cytology, albumin quotient, and immunoglobulin index.

**MACKAY:** Signs consistent with EPM and a positive result from a Western blot are consistent with the diagnosis. This assumes, of course, that the sample was obtained without significant blood contamination and that the blood-brain barrier is intact. A relative CSF quantity of  $\geq 5$  further supports the diagnosis. If the result is negative, EPM is unlikely, though several caveats need to be stated: (1) no one claims 100% sensitivity for this test—approximately one of ten horses with a negative test actually had EPM (confirmed histologically at necropsy) in a study performed by Dr. David Granstrom at the University of Kentucky<sup>12</sup>; (2) discordant results were obtained in almost 20% of cases when

individual samples were divided between two commercial laboratories in Lexington (based on a recent study conducted by the author); (3) horses with negative Western blots still may have EPM caused by *N. hughesi*. Other data from CSF cytology may (1) rule in other diseases (e.g., parasite migration, EEE, EHV1 myeloencephalopathy); (2) show mononuclear pleocytosis with increased protein concentration, which would support the diagnosis of EPM; or (3) be normal—this is the case in most instances of EPM.

**REED:** I interpret a positive Western blot in a horse with no evidence of blood contamination or evidence of disruption of the blood-CSF barrier as positive for EPM and place this horse on treatment.

**SUMMARY:** The Western blot is currently the best test for diagnosing EPM in horses. However, a positive CSF Western blot test in a normal horse is not reliable in predicting active disease. The test must be interpreted in light of the clinician's clinical and neurologic evaluation of the patient and the presence of blood contamination during CSF collection. Because the antibody test is not definitive for EPM, other testing—such as protein determination, RBC and WBC counts, cytology, albumin quotient, and immunoglobulin index—can be performed.

## QUESTION: *What is the value of determining that a horse has EPM when managing or treating it for EPM?*

**MACKAY:** This question contains a false premise because it is impossible to obtain a definitive diagnosis of EPM ante mortem. It is only important to obtain a good working diagnosis of EPM if (1) a delay in making an alternative (correct) diagnosis would prevent appropriate treatment—this may be true for a wobbler for which interbody vertebral fusion is contemplated or for a horse with temporohyoid osteoarthropathy in which a surgical procedure may need to be performed in a timely manner; or (2) treatment would impose a serious financial burden and would not be undertaken if the client knew that the disease was not treatable.

**REED:** Knowing whether a horse has EPM has several advantages, including initiation of appropriate therapy in a timely fashion, avoidance of drugs that

might produce toxic side effects, and expense. In addition, if a horse is treated for EPM when it actually has cervical vertebral stenotic myelopathy, it is detrimental for the horse to be walking with a compressive lesion that causes further damage to the spinal cord. In other words, regardless of the diagnosis it is always best to treat the correct condition.

**BERNARD:** The value of determining that a horse has EPM when considering management is critical to the long-term outcome of the case. If the patient is treated without diagnostics, other diseases may be overlooked. In addition, a large expense can be incurred while treating what may be the wrong disease. Although treatment is generally considered to be safe, there can be complications from therapy.

**ANDREWS:** There is always value in knowing what you are treating, whether it is EPM or any other disease affecting horses. Every effort should be made to arrive at a definitive diagnosis in every horse that is evaluated for EPM. Of course this is ideal, but I think it should be the goal in every case. I feel very strongly that clinicians should attempt to rule out other diseases before arriving at a diagnosis of EPM. Otherwise, if the diagnosis was not EPM, unresolved or persistent signs of EPM after management or treatment may be misinterpreted as a treatment failure. Also, in some cases horses may be treated for EPM but have another treatable disease. If the horse does not respond to EPM treatment, it may result in humane destruction, when in fact the horse had another treatable disease, such as vitamin E responsive degenerative myelitis or equine motoneuron disease. Also, if the horse has residual neurologic gait deficits, it is not known whether these deficits are a result of chronic EPM or some other disease. This may be true in horses with painful lameness, equine motoneuron disease, and vitamin responsive equine degenerative myelopathy.

Current management and treatment strategies for EPM are expensive and may lead to secondary complications. Current sulfadiazine-pyrimethamine preparations have been associated with diarrhea, anemia, leukopenia, and abortion in mares. Also, nitazoxanide treatment has been associated with depression, fever, and diarrhea. Also, the cost of EPM treatment is expensive, ranging from \$100 to \$1500/month, and long-term treatment may be indicated.

Furthermore, I recommend physical therapy for managing EPM, including lunging, ground jumping, light riding, and stretching after the second week of treatment. I feel that this helps produce a more rapid return to function. However, if another disease is present, physical therapy may be contraindicated. For example, lunging, ground jumping, and riding may worsen spinal cord compression and inflammation in horses with cervical stenotic myelopathy or spinal cord trauma. Thus physical therapy is contraindicated until the vertebrae are stabilized and spinal cord inflammation has subsided.

**FURR:** We should always strive to make a positive diagnosis whenever possible—whether it is EPM or another condition—it is simply good medicine. A definitive diagnosis allows the veterinarian to provide the most valuable counsel to the client regarding decisions about treatment and prognosis. If the diagnosis is not reasonably confirmed, it is hard to determine the duration of treatment or if treatment has been unsuccessful or effective. As we all know, certain circumstances arise in which everything you would like to do cannot be done; in these

situations the veterinarian should carefully consider the most likely differential diagnoses and at least try to rule them out.

**SUMMARY:** It is impossible to obtain a definitive diagnosis of EPM ante mortem. However, it is important to be as sure as possible for several reasons. If a horse is treated for EPM when it actually has cervical vertebral stenotic myelopathy, it is detrimental for the horse to be walking with a compressive lesion that causes further damage to the spinal cord. In addition, a large expense can be incurred while treating what may be the wrong disease. Also, a horse's lack of response to EPM treatment may result in humane destruction, when in fact the horse had another treatable disease. Finally, if the diagnosis was not EPM, unresolved or persistent signs of EPM after management or treatment may be misinterpreted as a treatment failure.

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