ANNE M. EBERHARDT

Although small in stature, the opossum packs a big punch when it comes to infecting Thoroughbreds with equine protozoal myeloencephalitis

Treatable Yet Difficult to Diagnose

EPM MIMICS OTHER NEUROLOGICAL DISEASES

By **AMANDA DUCKWORTH**

WHEN IT COMES to neurologic diseases in horses, three specific letters strike fear into the hearts of equine caregivers. EPM, which is short for equine protozoal myeloencephalitis, is a progressively debilitating disease that can affect any part of the horse's central nervous system, including from the front of the cerebrum to the end of the spinal cord.

EPM is widely held to be the most prevalent cause of neurologic disease in horses that reside in the American continents. Geography plays a role, as EPM is caused by an infection from the protozoan parasites Sarcocystis neurona, and, less commonly, Neospora hughesi.

The American Association of Equine Practitioners has published on its website comprehensive guidelines to assist practitioners with identification, diagnosis, and control of EPM.

"EPM is widely considered the most important infectious neurologic disease of horses in North America," said guidelines author Dr. Amy Johnson. "The variable clinical signs and widespread seroprevalence pose challenges to diagnosis. These guidelines aim to summarize essential information regarding this disease process, as well as highlight the three criteria for highest diagnostic accuracy in potentially affected horses."

The opossum is the definitive host for S. neurona. Horses can become infected when they ingest feed or water contaminated with opossum feces, and an estimated 50%-90% of horses in the United States have been exposed to the organism, but only a small percentage, usually less than 1%, develop EPM.

It is important that examinations and testing are done in order to determine if a horse is inflicted with EPM or a different neurologic disease that has similar clinical signs. EPM can mimic a number of other issues, but there are several points to help add clarity. As the AAEP explains, multifocal neurologic signs with asymmetric deficits (including ataxia) or muscle atrophy should increase clinical suspicion, while fever or evidence of pain accompanying the neurologic signs should decrease clinical suspicion.

If left untreated, EPM does get worse, and it can result in incoordination, weakness, muscle atrophy, difficulty swallowing, the inability to rise, and death. However, horses cannot pass EPM on to other horses.

Overall, about 60% to 70% of horses treated for EPM will improve significantly, but it is estimated that only 15% to 25% will recover completely. It is also estimated that relapse will occur in about 10%-20% of horses within two years. The earlier treatment is started, the better the odds of good results, and there are three treatments currently

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approved by the Food and Drug Administration for EPM.

In August 2022, the Veterinary Clinics of North America: Equine Practice published "Equine Protozoal Myeloencephalitis," which is a review of what is known about the disease.

"Since EPM was initially described in the 1960s, diagnosis, treatment, and prevention have improved through advances in the understanding of the parasite and the disease," explained researchers. "Epidemiologic studies have identified numerous risk factors associated with the development of the disease. Despite generally high seroprevalence of S. neurona in horses in the Americas, the annual incidence of EPM is less than 1%, thus demonstrating that infection does not equate with disease.

"Diagnosis of EPM has improved by detecting intrathecal antibody production against the parasite. Sulfadiazine/pyrimethamine (ReBalance) and the triazine compounds diclazuril (Protazil) and ponazuril (Marquis) are effective anticoccidial drugs that are now available as FDA-approved treatments for EPM."

Diagnosing neurological issues in horses does not completely stop at S. neurona or N. hughesi. In June 2023, Veterinary Parasitology published "Evidence of intrathecally-derived antibodies against Toxoplasma gondii in horses suspected of neurological disease consistent with equine protozoal myeloencephalitis."

"Among the recognized neurologic diseases in horses, EPM has been reported around the world and still presents challenges in diagnosis and treatment," explained researchers. "Horses can present with clinical neurologic signs consistent with EPM while testing negative for the two main causative agents, S. neurona or N. hughesi, and may still be clinically responsive to anti-parasitic drug therapy. This context led to our hypothesis that another protozoal parasite, Toxoplasma gondii, which is known to cause toxoplasmosis in other mammalian species, is a potential pathogen to cause neurologic disease in horses."

For the study, researchers collected serum and cerebrospinal fluid (CSF) from 210 horses presenting with clinical signs compatible with EPM, and the indirect immunofluorescent antibody

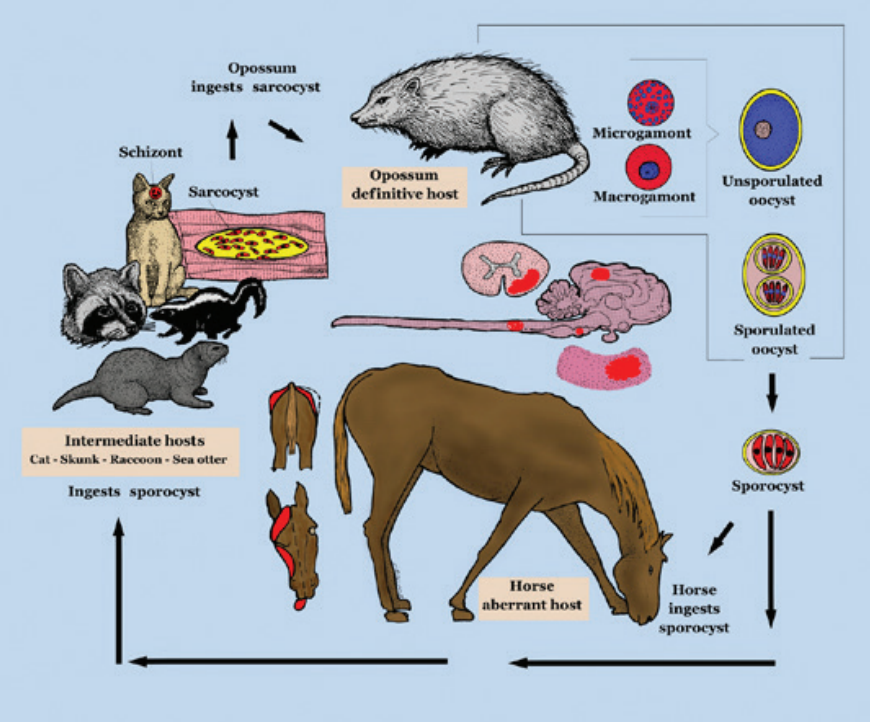
test (IFAT) was used to detect antibody titers for T. gondii, S. neurona, and N. hughesi.

According to researchers, 133 (63.3%) horses were positive for serum T. gondii antibodies using a cutoff titer of 160, and 31 (14.8%) positive for CSF T. gondii antibodies using a cutoff titer of 5. Furthermore, 21 (10.0%) of EPM-suspect horses had a serum:CSF ratio ≤ 64 for antibodies for T. gondii, while 43 (20.5%) and 8 (3.8%) horses had a serum to CSF ratio ≤ 64 for antibodies for S. neurona and N. hughesi, respectively.

"This study showed the presence of antibodies against T. gondii, S. neurona, and N. hughesi in the CSF of horses with neurological signs compatible with EPM," concluded researchers. "There was no difference in the clinical presentation among horses with laboratory results suggestive of intrathecally-derived antibodies to T. gondii and the ones with evidence of S. neurona and/or N. hughesi infection (etiological agents of EPM). This finding supports the hypothesis that T. gondii could be associated with neurologic disease compatible with EPM.

"We recommend broadening the diagnostic suite of laboratory tests to be used on EPM-suspect horses to include T. gondii serology of serum and CSF, especially when clinical horses test negative for S. neurona and N. hughesi. To further characterize the importance of T. gondii as a causative agent of neurologic disorder in horses, more studies need to be performed to investigate possible lesions produced by T. gondii in the central nervous system and the presence of the parasite itself, as well as correlating it with antibody titers in serum and CSF for the same infectious agent."

Finding ways to differentiate EPM from other neurologic diseases during diagnosis is important. In December 2021, Veterinary Immunology and Immunopathology published "Horses affected by EPM have increased sCD14 compared to healthy horses."



The life cycle of EPM definitively begins with opossums

"EPM is a debilitating neurologic disease affecting horses across the Americas," explained researchers. "Gaps in understanding the inflammatory immune response in EPM-affected horses create difficulties with diagnosis and treatment, subsequently negatively impacting the prognosis of affected horses. The purpose of the current study was to evaluate circulating levels of the inflammatory immune marker soluble CD14 (sCD14), in horses with EPM and determine if they differed from healthy neurologically normal horses."

Paired sera and CSF samples were analyzed by researchers for sCD14. To be included in the study, EPM horses had to meet certain criteria, which consisted of the presence of neurologic signs consistent with EPM, S. neurona surface antigens 2, 4/3 (SnSAG 2, 4/3) ELISA serum:CSF antibody ratio ≤ 100, and a postmortem diagnosis of EPM. The control horses were neurologically normal.

"Serum anti-S. neurona antibodies indicate that healthy control horses were exposed to S. neurona but resistant to developing clinical EPM," researchers concluded. "EPM cases had significantly greater concentrations of sCD14 in CSF samples compared to control horses and increased serum sCD14 concentrations.

"A positive correlation between sCD14 serum and CSF concentrations was observed in EPM-affected horses but not healthy horses. Soluble CD14 is an inflammatory marker, and the study results suggest it is elevated in EPM patients. When performed in conjunction with clinical evaluation and standard antibody testing, there may be potential for sCD14 to be utilized as a correlate for EPM."

Because diagnosing EPM is not straightforward, research continues to be done on how to distinguish it from other potential neurologic issues. However, studies on the topic can result in conflicting information.

For example, in March 2021, Veterinary Parasitology published "Molecular detection of Sarcocystis neurona in cerebrospinal fluid from 210 horses with suspected neurologic disease."

WIKIMEDIA COMMONS

One component of diagnosing EPM is for veterinarians to conduct physical neurological tests. It's a tricky disease to verify but utilizing both serum and CSF SarcoFluor as adjuncts to immunofluorescent antibody testing can help rule out other neurological disorders

"An ante-mortem diagnosis of EPM is presently based on clinical presentation, immunodiagnostics performed on serum and cerebrospinal fluid (CSF), and ruling out other neurological disorders," explained researchers. "Molecular techniques introduce a novel and promising approach for the detection of protozoal agents in CSF."

In all, 210 CSF samples from horses suspected of neurological disease with EPM included as a differential diagnosis were tested using rtPCR as part of the study. Researchers then compared molecular and immunological results with respect to the origin of the horse, time of the year, signalment, clinical signs, and treatment history. They concluded 25 horses tested positive in CSF for S. neurona by rtPCR only, while 30 horses had intrathecally-derived antibodies to S. neurona only, and 13 horses tested rtPCR-positive in CSF with evidence of intrathecally-derived antibodies to S. neurona.

"Previous treatment for EPM was the only variable presenting statistical difference between the two testing modalities, highlighting that animals with history of anti-protozoal treatment were more likely to test positive solely in IFAT, while horses without treatment were more likely to test positive by rtPCR only," researchers concluded. "The results support the use of molecular diagnosis for EPM caused by S. neurona as a complement to immunodiagnostics. The use of rtPCR in CSF for the detection of S. neurona may improve the diagnostic work-up of neurologic disease suspected horses, especially in animals without previous anti-protozoal treatment."

However, the September/October 2023 edition of the Journal of Veterinary Internal Medicine published "Evaluation of real-time polymerase chain reaction for the diagnosis of protozoal myeloencephalitis in horses using cerebrospinal fluid."

"EPM caused by Sarcocystis neurona remains an antemortem diagnostic challenge in some horses," explained researchers. "Recent work suggested the use of real-time PCR (rtPCR) on cerebrospinal fluid (CSF) as a promising

Symptom Checklist from the American Association of Equine Practitioners

For assessing the possibility of EPM:

- **Ataxia** (incoordination), spasticity (stiff, stilted movements), abnormal gait or lameness.
- **Incoordination** and weakness which worsens when going up or down slopes or when head is elevated.
- **Muscle atrophy,** most noticeable along the topline or in the large muscles of the hindquarters, but can sometimes involve the muscles of the face or front limbs.
- **Paralysis** of muscles of the eyes, face, or mouth, evident by drooping eyes, ears, or lips.
- **Difficulty swallowing.**
- **Seizures or collapse.**
- **Abnormal sweating.**
- **Loss of sensation** along the face, neck, or body.
- **Head tilt** with poor balance; horse may assume a splay-footed stance or lean against stall walls for support.

STEPHANIE CHURCH

diagnostic tool. The objective of this study was to evaluate the sensitivity and specificity of S. neurona rtPCR on CSF for EPM diagnosis using horses with EPM and S. neurona-seropositive horses with other neurologic conditions."

This was a retrospective case-control study using banked CSF samples. It featured 99 horses with neurologic disease that underwent complete neurologic examination, CSF collection, and, if euthanized, necropsy including the central nervous system (CNS). In all 52 horses had EPM, 23 of which were confirmed via necropsy and 29 of which were clinical diagnoses.

"The other 47 horses all had necropsy-confirmed diagnoses," researchers concluded. "Four of the 47 horses had normal neurologic findings on necropsy and the remaining 43 horses had neurologic diseases including equine degenerative myeloencephalopathy (EDM), cervical vertebral stenotic myelopathy, trauma, and other miscellaneous conditions. One CSF sample was weakly positive for S. neurona by rtPCR, this sample was obtained from a horse with confirmed EDM. Samples from the other 98 horses were negative for S. neurona by rtPCR.

"Our study contradicts previous conclusions that S. neurona rtPCR is potentially useful for EPM diagnosis, because our results indicate that the assay has a low sensitivity (0%) for EPM."

In August 2024, Veterinary Parasitology published "A fresh look at the SarcoFluor antibody test for the detection of specific antibodies to Sarcocystis neurona for the diagnosis of equine protozoal myeloencephalitis."

"EPM is a challenging disease to diagnose in horses with neurological signs," explained researchers. "To optimize contemporary diagnostic testing, including the use of serum:CSF antibody ratios, the SarcoFluor antibody test for Sarcocystis neurona requires revalidation. The SarcoFluor, a previously validated immunofluorescent antibody test (IFAT) for the detection of antibodies specific to S. neurona in serum and cerebrospinal fluid (CSF) of naturally infected horses was analyzed using recent data and considering a serum:CSF antibody ratio threshold. Utilization of serum and CSF phosphorylated neurofilament heavy protein (pNfH) concentrations in support of an EPM diagnosis was also evaluated."

For the study, data on 172 horses presented to an equine veterinary hospital in California were divided into three groups. There were 42 EPM-positive horses, 74 neurological non-EPM horses confirmed with non-EPM neurological diseases, and 56 control horses. Researchers used logistic regression to compare EPM diagnostic regimens, meaning EPM+ horses were compared with neurological non-EPM horses showing neurological signs.

"To consider diagnostic utility, post-test probabilities were calculated by titer," explained researchers. "When differentiating between EPM and other neurological diseases, the combination of serum and CSF SarcoFluor testing added more information to the model accuracy than either test alone. Using serum and CSF for pNfH in support of an EPM diagnosis did not identify cut-offs with statistically significant odds ratios but increased the overall model accuracy when used with the IFAT. Utilization of IFAT titers against S. neurona in serum and CSF result in a high post-test probability of detecting EPM+ horses in a clinical setting."

EPM can have a devastating impact on a horse. Working with a veterinarian to properly diagnose and treat the disease as early as possible remains vitally important. BH