EPM in Horses:
Causes, Diagnosis, Treatment and Management

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Equine Protozoal Myeloencephalitis (EPM) is a focal or multifocal central nervous system (CNS) disease that can affect the brain and spinal cord. It can be caused by either *Sarcocytis neurona* or *Neospora hughesi*, but most cases are due to infection with *S. neurona*.

Etiology:
S. neurona has a 2-host life cycle and multiple intermediate hosts, which include skunks, raccoons, armadillos and cats. The opossum has been identified as the definitive host. The parasite reproduced in the intestinal epithelium of the opossum resulting in production of sporozoites, which contain the sporocysts that are passed in the feces. Sporozoites are infectious to the intermediate hosts. Latent sarcocysts are developed in the muscle tissue of the intermediate host, which is the source of infection for the opossum. Opossums will contaminate the environment through passage of contaminated feces. Horses will get infected by ingestion of contaminated food or water sources with opossum fecal material. It is important to recognize that there is no horizontal transmission between horses, and it cannot be transmitted to non-equine intermediate hosts. Even though vertical transmission of the organism is uncommon there have been a few reports of infected foals prior to suckling. [1,2]. The exact mechanism through which the organism enters the CNS is poorly understood, but it is suspected to be through infection of endothelial cells or leukocytes.

The complete life cycle of *N. hughesi* is not completely known. Canids are the definitive host for *Neospora caninum,* but it is still not confirmed that dogs or wild canids are the definitive host for *N. hughesi*. *N. caninum* can be transmitted vertically in cattle and there have been several reports showing that the organism can be transmitted transplacentally in horses.[3,4.]

All horses and equids are susceptible to being infected with EPM, but not all horses will develop disease, which has been demonstrated by multiple studies in mice and horses which have shown the importance of the immune response in preventing development of disease. It is not completely clear what factors are involved in progression to neurologic disease, as studies looking at stress and administration of immunosuppressive doses of steroids did not consistently cause an increase in severity of neurologic disease. [5,6].

Epidemiology and Risk Factors:
Thoroughbreds, Standardbreds and Quarter Horses have been most commonly reported, but the disease can happen in any breed of horse.[5] Seroprevalence of *S. neurona* can have a very large variability depending on geographical location[7-11], while *N. hughesi* usually has a low seroprevalence.
EPM is typically an individual horse disease, but there have been clusters of cases identified.[12,13]. Most studies have found that young horse (1-5 years) and older horses (>13 years) have a higher risk of development of the disease. The least common season for occurrence of EPM is winter, while the risk in spring and summer is 3x higher and 6x higher in the fall. Other risk factors associated with development of EPM are the presence of opossums, previous diagnosis of EPM, and presence of wooded areas.

Stressful events such as transportation[14], heavy exercise, trauma, surgery or parturition have been associated with high risk of development of EPM[15]. Race and show horses have been demonstrated to be at higher risk of development of EPM compared to pleasure and breeding horses.

Clinical Signs:

There is a large amount of variability in clinical signs, which can be acute or chronic, local, or multifocal and involving the brain, brainstem, or spinal cord. Dysphagia, abnormal upper airway function, unusual or non-specific lameness, or even seizures can be signs of EPM. Horses that are severely affected can present with difficulty rising, walking, or swallowing and the clinical signs will rapidly progress. The main reason why there is so much variability in clinical signs is because it will depend on if white or grey matter are affected and on the affected site. Grey matter signs involve focal muscle atrophy and severe muscle weakness, while white matter lesions usually cause ataxia and weakness in the limbs caudal to the site of infection. Initial clinical signs include stumbling or interference, which can be easily confused with a subtle lameness. Affected horses can have a gradual onset that will rapidly progress to severe clinical disease and recumbency. Neurologic evaluation of affected horses usually reveals asymmetric ataxia, weakness, and spasticity. Common clinical signs of brain or brainstem disease are obtundation, head tilt, facial nerve paralysis and difficulty swallowing amongst others.

Differential Diagnosis:

EPM affected horses can have very similar clinical signs to a lot of neurologic diseases. It is imperative to perform a complete and thorough neurologic examination to differentiate between these neurologic diseases. Common differentials include cervical vertebral myelopathy (CVM), trauma, EHV-1, WNV encephalomyelitis, equine degenerative myeloencephalopathy (EDM), equine motor neuron disease (EMND), spinal cord tumors, toxicities, temporohyoid osteoarthropathy, metabolic derangements and hepatic encephalopathies amongst others[11].

Diagnosis:

For antemortem diagnosis it is important to perform a thorough neurologic evaluation and to rule out other potential causes for the presence of neurologic signs. Cervical radiography could be of value to rule out the presence of other conditions that could affect the nervous system. Immunodiagnostic tests in serum and CSF can aid in the diagnosis of the disease.[16] Detection of serum antibodies in horses infected with *S. neurona* does not confirm the presence of disease, just exposure to the organism. Testing for serum antibodies against *S. neurona* has minimal diagnostic value unless the results are negative, but on the other hand detection of serum antibodies for *N. hughesi* in a neurologic horse has a much higher positive predictive value due to the low seroprevalence of the organism. It is important to remember that a negative serum test in an early infected neurologic horse does not rule out the possibility of EPM, and it is recommended to retest in 10-14 days. Detection of antibodies in the CSF can provide more valuable information, but it is important to remember that by itself it is not a positive indicator of disease, as there is the possibility of antibodies to cross a healthy blood brain barrier or have blood contamination form sample collection. It is for this reason that a serum:CSF ratio should be performed when infection with *S. neurona* is suspected. Unfortunately, a cutoff ratio for infection with *N. hughesi* has not been established at this time.

Available tests for *S. neurona*:

- Western blot (WB)
    - Qualitative test – detects antibodies against merozoite lysate.
    - High negative predictive value
- Indirect fluorescent antibody testing (IFAT)
    - Quantitative test – detects antibodies against culture-derived whole merozoites.
    - Poor predictor of EPM when used alone.
- Surface Antigen Enzyme-linked immunosorbent assay (SAG ELISA)
    - SnSAG2 ELISA and SnSAG 4/3 ELISA
    - Quantitative test – detects *S. neurona* surface antigens.
    - Used on both serum and CSF samples.

Available test for *N. hughesi*:

- Surface Antigen Enzyme-linked immunosorbent assay (SAG ELISA)
    - NhSAG1 – detects surface antigens.
        - 94% sensitivity, 95% specificity
    - IFAT – detects antibodies against whole *N. hughesi* tachyzoites.
        - 100% sensitivity, 71.4% specificity

Postmortem diagnosis with H&E staining, can in a small percentage (10-36%) of cases show CNS lesions caused by protozoa [17,18]. Significant inflammatory changes are usually present, and there is experimentally a PCR test to detect parasites in CNS tissue.

Treatment:

- Ponazuril (Marquis®)
- Diclazuril (Protazil®)
- Sulfadiazine/Pyrimethamine (ReBalance®)

Supportive medical treatment:

- NSAID's
- Corticosteroids
- DMSO
- Vitamin E

Immunomodulators

- Levamisole
- Killed Propionibacterium agnes (EqStim™)
- Mycobacterial wall extract (Equimune ®)
- Inactivated Parapox ovis virus (Zylexis)
- Transfer Factor (4Life® Transfer Factor)

Prevention:

The main preventative approach to EPM is decreasing stress and reduction of exposure to opossum feces, which can be achieved by not feeding horses off the ground, provide separate sources of fresh water to horses and preventing wildlife from entering the paddocks and stalls of horses will help minimize the incidence of infection.

There are reports of intermittent use of coccidiostatic and coccidiocidal drugs to prevent EPM. [19,20.] A study looking at a dose of 2.5 or 5mg/kg PO q 24 hrs. for 7 days before experimental challenge and then continued for 28 days showed decreased clinical signs and delayed seroconversion. In another study, intermittent administration of ponazuril paste at a dose of 20mg/kg PO every 7 days showed decreased intrathecal *S. neurona* antibody response in experimentally infected horses. Neither of these studies eliminate the risk of infection. Another study, looking at low dose Diclazuril (0.5 mg/kg PO, q 24 hrs.) administered to foals in a farm with high exposure rate to *S. neurona* showed a significant reduction in seroprevalence in treated versus untreated foals[21].

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