Equine Protozoal Myeloencephalitis (EPM)

Definition

Equine protozoal myeloencephalitis (EPM) is a neurologic disease of horses caused by protozoal infection of the central nervous system. *Sarcocystis neurona* causes most cases; *Neospora hughesi* can also cause disease. Both organisms are obligate intracellular pathogens in the protozoan phylum Apicomplexa.

Clinical Signs

Clinical signs are variable and can mimic most other neurologic diseases as well as musculoskeletal problems. This variability occurs because the parasite can affect both white and gray matter randomly at one or multiple sites within the central nervous system (CNS). Clinical signs reflect affected areas of the spinal cord and brain and can include ataxia, weakness, muscle atrophy, unusual or atypical lameness, reduced or absent sensation, alterations in level of consciousness or behavior, and cranial nerve deficits such as dysphagia, facial paralysis, and ocular abnormalities. EPM is often progressive but can have an acute or insidious onset. The progression can be rapid, or the clinical signs might appear to stabilize only to relapse or worsen later.

While EPM can mimic many diseases, certain clinical signs increase or decrease suspicion for EPM. 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.

Incubation Period

The time from sporocyst ingestion to clinical disease is unknown; the pathogenesis of *S. neurona* in horses is unclear due to the lack of an experimental model that reliably induces disease.

Risk Factors

All horses are considered susceptible to EPM, but most horses exposed to the causative organisms never show signs of disease. A horse's individual immune response and variation in protozoal inoculum (protozoal strain, dose, frequency) likely determine whether infection is controlled or progresses to neurologic disease. Young age (1-5 years old), old age (>13 years), breed (Thoroughbred, Standardbred, and Quarter Horse), and season (spring, summer, fall) have all been identified as risk factors in some studies. Stressful events such as heavy exercise, transport, injury, surgery, and parturition are also thought to increase risk.

Opossums are commonly infected with *S. neurona*, and substantial environmental contamination occurs in locations where opossums are frequently observed, increasing risk of equine exposure and disease. Previous diagnosis of EPM and presence of woods have also been reported as risk factors, while preventing wildlife access to feed and having a natural water source for wildlife are considered protective.

Transmission

The opossum (*Didelphis virginiana* in North America and *D. albiventris* in South America) is the definitive host for *S. neurona*. Intermediate hosts include skunks, raccoons, sea otters, cats, and armadillos. During the normal life cycle of *S. neurona*, opossums excrete sporocysts in feces, which are then consumed by intermediate hosts. Sporozoites excyst in the intestine and parasitemia develops, followed by schizont formation in various tissues. Sarcocysts eventually form in muscles of intermediate hosts, and opossums are subsequently infected by consumption of muscle tissue containing sarcocysts.

Horses are considered aberrant (incidental), dead-end hosts for *S. neurona*. Like intermediate hosts, horses are infected by consuming food or water contaminated with opossum scat containing sporocysts. In naturally infected horses with neurological signs, *S. neurona* schizonts have been found only in the central nervous system, apart from one young foal reported to have muscle sarcocysts. Since horses generally do not develop muscle sarcocysts like intermediate hosts, horses are not considered to play an important role in the life cycle of this organism.

The life cycle of *N. hughesi* has not been completely characterized, and the mode(s) of transmission of *N. hughesi* to horses remains unclear. Vertical (transplacental) transmission from mare to foal has been described.

Diagnostic Sampling, Testing and Handling

Highest accuracy in antemortem diagnosis is obtained by fulfilling 3 criteria: (1) confirmation of clinical signs consistent with spinal cord or brain dysfunction through careful clinical neurologic examination, (2) exclusion of other potential causes of these signs using appropriate diagnostic testing, and (3) immunodiagnostic (serologic) testing on paired serum and CSF samples to confirm intrathecal antibody production against *S. neurona* or *N. hughesi*.

If the horse shows clinical signs of neurologic disease and other potential causes are excluded or considered less likely, EPM testing is recommended. All commercially available tests are suitable for testing serum, CSF, or both. Blood and CSF should be collected in red-top (no additive) tubes and serum separated. Samples can be kept refrigerated or frozen until submission. Currently available tests for *S. neurona* include Western blot (WB), enzyme-linked immunosorbent assays (SnSAG 2, 4/3 ELISA; SAG 1, 5, 6 ELISA), and indirect fluorescent antibody test (IFAT). Currently available tests for *N. hughesi* include ELISA and IFAT.

General principles for interpretation of EPM test results are as follow:

- A positive serum test indicates exposure to the organism but does not confirm CNS infection, regardless of the magnitude of the titer. Therefore, particularly in areas where exposure is common, a positive serum test will have a low positive predictive value for CNS infection and clinical disease. Serologic screening of normal animals is not recommended.
- A negative serum test usually indicates that the horse has not been exposed to the organism. Therefore, a negative serum test generally has a high negative predictive value for clinical disease, meaning that a negative result is very useful in excluding EPM as the cause of disease. Rarely, a recently infected horse might show clinical signs prior to seroconversion, in which case repeated testing in 10-14 days should yield positive results.
- A positive CSF test is more likely to correlate with an EPM diagnosis than a positive serum test. However, false positives commonly occur due to normal diffusion of antibodies across the blood-brain barrier or blood contamination of samples. Horses with low CSF titers are less likely to have EPM than horses with high CSF titers.
- A negative CSF test usually means EPM is not the cause of disease. Rarely, as mentioned above, a recently infected horse will show clinical signs prior to developing a measurable antibody level in CSF; re-testing 10-14 days later should yield positive results.
- The most accurate way to diagnose EPM is to submit serum and CSF for quantitative testing and calculation of a serum:CSF titer ratio or specific antibody index, allowing detection of intrathecal antibody production. Validation studies for the *S. neurona* SAG 2, 4/3 ELISA showed that the serum:CSF titer ratio increased overall test accuracy to 93-97%, as opposed to serum alone, which had an overall accuracy of 54-56%.

Post-mortem

Typical post-mortem lesions are limited to the central nervous system. Lesions are sometimes grossly visible as well-demarcated discolored areas or even hemorrhagic destruction of portions of the brain or spinal cord. Typical histologic lesions include mononuclear perivascular inflammation, parenchymal necrosis with phagocytosis and gitter cell formation, astrocyte proliferation, and gemistocyte formation. Eosinophils and multinucleated giant cells are seen commonly. Inflammation is more predominant in acute cases, while chronic cases often show minimal inflammatory response but more tissue destruction, astrocyte proliferation, and fiber degeneration. Parasites are not reliably observed in lesions, particularly in chronic cases or in horses that have received anti-protozoal treatment. Immunohistochemical techniques improve detection of parasites. It is important to note that lesions are not uniformly distributed throughout the CNS, and routine post mortem survey samples might fail to detect small lesions.

Shedding of Organism Following Resolution of Clinical Signs	Horses do not shed organism during or after clinical disease. However, recrudescence of disease with reappearance or worsening of neurologic signs after resolution or substantial improvement happens in a proportion of cases. It is unclear whether disease recrudescence represents re-infection of a susceptible horse or failure of treatment to clear the organism.
Environmental Persistence	Horses are considered aberrant hosts for *S. neurona* and do not spread disease. *S. neurona* sporocysts excreted by opossums can persist in the environment.
Specific Control Measures	Preventative approaches for EPM include prophylactic administration of anti-protozoal drugs, reducing exposure by minimizing contact with opossum scat, and improving equine immune defenses by decreasing stress and optimizing health. Prophylactic administration of anti-protozoal drugs such as ponazuril and diclazuril has been investigated in several studies. Various dosages and dosing intervals were utilized with similar results, including delayed seroconversion, reduced intrathecal antibody response, and reduced clinical signs. These studies indicate that prophylactic anti-protozoal treatment using various protocols minimizes but does not eliminate infection in horses experimentally or naturally exposed to *S. neurona*. A "standard" prophylactic protocol has not been established, and the relatively low incidence of disease combined with cost of prophylactic treatment means that prophylactic treatment is likely to be reserved for high-risk horses in high-risk environments. Eliminating access of opossums to feed and water is recommended by keeping grains in rodent-proof containers and forages in enclosed facilities. An effective vaccine has not been developed.
Biosecurity Issues for Receiving Animals	Horses with EPM do not present a biosecurity risk to other animals because the disease is not transmissible between horses. Opossums, the only known definitive hosts for *S. neurona*, are found only in the Americas. Therefore, horses imported from other countries to the Americas should have no previous exposure to *S. neurona* and should be seronegative. However, horses exported from the Americas to other countries might have been exposed previously to *S. neurona* or be actively infected; in both scenarios the horse is likely to be seropositive. These seropositive horses do not pose a risk to other animals but could individually succumb to disease after export.
Disinfection	Horses with EPM are not contagious and do not pose a risk to neighboring horses. Disinfection is not necessary for areas or objects in contact with affected horses.
Zoonotic Potential	None. Humans are not susceptible to *S.neurona* or *N. hughesi*.

Further reading	Equine Protozoal Myeloencephalitis: An Updated Consensus Statement with a Focus on Parasite Biology, Diagnosis, Treatment, and Prevention S.M. Reed, M. Furr, D.K. Howe, A.L. Johnson, R.J. MacKay, J.K. Morrow, N. Pusterla, S. Witonsky. First published: 09 February 2016; Citations: 38

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