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Overview of Equine Protozoal Myeloencephalitis

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Equine protozoal myeloencephalitis (EPM) is a common neurologic disease of horses in the Americas; it has been reported in most of the contiguous 48 states of the USA, southern Canada, Mexico, and several countries in Central and South America. In other countries, EPM is seen sporadically in horses that previously have spent time in the Americas.

Etiology and Epidemiology:

Most cases of EPM are caused by an Apicomplexan protozoan, *Sarcocystis neurona*. Horses are infected by ingestion of *S neurona* sporocysts in contaminated feed or water. The organism undergoes early asexual multiplication (schizogony) in extraneural tissues before parasitizing the CNS. Because infectious sarcocysts are only rarely formed, the horse is considered an aberrant, dead-end host for *S neurona*. Like other *Sarcocystis* spp, *S neurona* has an obligate predator-prey life cycle. The definitive (predator) host for *S neurona* in the USA is the opossum (*Didelphis virginiana*). Opossums are infected by eating sarcocyst-containing muscle tissue from an infected intermediate (prey) host and, after a brief prepatent period (probably 2–4 wk), infectious sporocysts are passed in the feces. Nine-banded armadillos, striped skunks, raccoons, sea otters, Pacific harbor seals, and domestic cats have all been implicated as intermediate hosts; however, the importance in nature of each of these species is unknown. Sporadic cases of EPM are associated with *Neospora hughesi*, an organism closely related to *S neurona*. The natural host(s) of this organism have not yet been identified.

Clinical Findings:

Because the protozoa may infect any part of the CNS, almost any neurologic sign is possible. The disease usually begins insidiously but may present acutely and be severe at onset. Signs of spinal cord involvement are more common than signs of brain disease. Horses with EPM involving the spinal cord have asymmetric or symmetric weakness and ataxia of one to all limbs, sometimes with obvious muscle atrophy. When the sacrocaudal spinal cord is involved, there are signs of cauda equina syndrome. EPM lesions in the spinal cord also may result in demarcated areas of spontaneous sweating or loss of reflexes and cutaneous sensation. The most common signs of brain disease in horses with EPM are depression, head tilt, and facial paralysis. Any cranial nerve nucleus may be involved, and there may be seizures, visual deficits including abnormal menace responses, or behavioral abnormalities. Without treatment, EPM may progress to cause recumbency and death. Progression to recumbency occurs over hours to years and may occur steadily or in a stop-start fashion.

Lesions:

There is focal discoloration, hemorrhage, and/or malacia of CNS tissue. Histologically, protozoa may be found in association with a mixed inflammatory cellular response and neuronal destruction. Schizonts, in various stages of maturation, or free merozoites commonly are seen in the cytoplasm of neurons or mononuclear phagocytes. Also parasitized are intravascular and tissue neutrophils and eosinophils and, more rarely, capillary endothelial cells and myelinated axons. Merozoites may be found extracellularly, especially in areas of necrosis. In at least 75% of clinical cases, protozoa are not seen on H&E-stained sections.

Diagnosis:

Postmortem diagnosis is confirmed by demonstration of protozoa in CNS lesions on the basis of distinctive morphology or by immunohistochemical staining. Testing for *S neurona*–specific antibody is the basis for presumptive antemortem diagnosis of EPM. Serologic tests for specific antibodies against whole *S neurona* (eg, indirect fluorescent antibody test) or *S neurona* surface antigens (snSAGs) provide evidence of current or recent exposure to the organism; thus, low or negative serum titers tend to exclude the diagnosis of EPM. Conversely, positive or high serum *S neurona* titers have limited diagnostic utility in that such titers do not clearly

distinguish horses with subclinical extraneural infections from those with EPM. In horses with neurologic signs, serum:CSF antibody titer ratios of <1:100 or *C*-ratios >1 are indicative of production of *S neurona* antibody in the CNS and are highly supportive of the diagnosis of EPM. In a few horses with EPM, CSF analysis reveals abnormalities such as mononuclear pleocytosis and increased protein concentration.

Depending on the clinical signs, differential diagnoses may include cervical vertebral stenotic myelopathy, trauma, aberrant parasite migration, equine degenerative myeloencephalopathy, equine herpesvirus 1 myeloencephalopathy, equine motor neuron disease, cauda equina neuritis, arboviral (Eastern or Western equine, West Nile) encephalomyelitis, rabies, bacterial meningitis, hepatoencephalopathy, and leukoencephalomalacia.

Treatment:

The FDA-approved treatments for EPM are ponazuril (5 mg/kg/day, PO, for 28 days), diclazuril (1 mg/kg/day, PO, for 28 days), and a combination of sulfadiazine and pyrimethamine (20 mg/kg and 1 mg/kg, respectively, for at least 90 days). The bioavailabilities of ponazuril and diclazuril are improved by concurrent PO administration of corn oil or DMSO. A loading dose of ponazuril (15 mg/kg, PO) may be given on the first day of treatment to rapidly attain therapeutic blood levels. The sulfadiazine/pyrimethamine product must be given at least 1 hr before or after hay is fed. Anemia may develop after prolonged treatment with sulfadiazine/pyrimethamine and is best prevented by providing folate-rich green forage such as alfalfa hay or green pasture. Approximately 60% of horses improve with each type of treatment, but <25% recover completely. Relapses occur commonly up to 2 yr after discontinuation of antiprotozoal therapy. Because immunosuppression/immunodeficiency may be a risk factor for EPM, immunomodulators (eg, mycobacterial cell-wall derivative, levamisole, killed parapox ovis, or transfer factor) are sometimes given as ancillary therapy.

Prevention and Control:

No proven preventive is available. A conditionally approved vaccine was marketed, but the license lapsed in 2008 and it is no longer offered. There is interest in using antiprotozoal drugs for prevention; however, evidence-based protocols are not yet available. The source of infective sporocysts is opossum feces, so it is prudent to prevent access of opossums to horse-feeding areas. Horse and pet feed should not be left out; open feed bags and garbage should be kept in closed galvanized metal containers, bird feeders should be eliminated, and fallen fruit should be removed. Opossums can be trapped and relocated. Because putative intermediate hosts cannot be directly infective for horses, it is unlikely that control of these populations will be useful in EPM prevention.