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Equine Protozoal Myeloencephalitis - An Updated View on the Epidemiology, Accurate Diagnosis and Treatment of Disease: A Review

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Abstract

Equine protozoal myeloencephalitis (EPM) is considered to be significant parasitic disease of equines. The disease is considered to be caused by 2 protozoa unicellular parasites: Sarcocystis neurona and Neospora hughesi respectively. It is important note that the myeloencephalitis does not show pathognomical signs, and thus it is very hard to be diagnosed before the fatal exit. The horses that are affected develop multifocal central nervous system disease. Breed, age and transport stress have been claimed as a predisposing factors that play crucial role. Nevertheless the same cannot be said about the virulence and other specifics about the parasite.

Keywords: *Equine Protozoal Myeloencephalitis, Sarcocystis Neurona, Neospora Hughesi, Parasitic Disease.*

INTRODUCTION

The syndrome "Equine protozoal myeloencephalitis (EPM)" was firstly named "Focal encephalitis-myelitis" due to disease brain involvement (1). Protozoa casual agents were initially observed in connection with characteristic lesions in 1974, and the illness was dubbed Equine Protozoal Myeloencephalitis. EPM was initially referred to as "Segmental myelitis". Many cases were described in 1968 and 1970. It is now firmly established that EPM can be caused by either *Sarcocystis neurona or Neospora hughesi*, although the majority of occurrences are attributed to infestation with *S. neurona* (2-6).

EPIDEMIOLOGY

A survey in the North America found that EPM cases appeared in horses with age 4 years or younger, with fewer cases in horses over 6 years old (7). Another study indicated that male horses were at the highest risk. The seroprevalence of *S. neurona* in the U.S. ranged from 15% to 89% and was around 35.6% in Brazil and Argentina. *N. hughesi* infestation was less common. EPM was least common in winter and more frequent in spring, summer, and fall. Factors like the presence of opossums, a previous EPM diagnosis, and wooded areas increased the risk of EPM. Preventing wildlife from accessing feed and using a creek or river as a water source reduced the risk. Stress and age-related immune suppression also increased the risk (8). Treating EPM with anticoccidial drugs greatly improved recovery chances.

TRANSMISSION, LIFE CYCLE AND MODES OF INFECTION

Sarcocystis neurona protozoa has a two-part life cycle, involving a specific host and other animals species between (9). In North America, opossums are the main hosts, while in South America, other species of marsupials playing this role. The parasite reproduces in the intestines of infected opossums, releasing tiny forms called sporozoites in their feces. These sporozoites can infect other animals like skunks, raccoons, armadillos, and even cats. Inside these animals, the parasite forms small pockets called sarcocysts in their muscles. When opossums eat the contaminated meat of these infected animals, they become hosts of parasite again, continuing the life cycle of protozoa. Opossums are the most common carriers of this parasite and can spread it widely (10).

Equine receive *S. neurona* infestation by per oral mode of infestation with contaminated food or water from opossum carrier faeces. Although *S. neurona* has been found in one case of a young foal with EPM symptoms, horses likely aren't normal hosts for this parasite (11). Opossums are the main source of *S. neurona* infestation for horses. How exactly *S. neurona* enters the CNS is unknown, but it likely involves infecting endothelial cells or leukocytes (12 - 15). The full life cycle of *N. hughesi* is unclear at the moment, and it's not confirmed that dogs or wild canids playing role as definitive hosts. It is sure that all horses can get EPM but not all infested horses develop the clinical disease (16-19). The

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immune response plays a key role in preventing EPM, but the exact mechanisms of disease pathogenesis are still unclear. Factors like stress and variations in parasite exposure may contribute to EPM, but treating infected horses with immunosuppressive drugs doesn't necessarily worsen the disease. Genetic differences and those of parasite virulence among *S. neurona* strains exist, but it's uncertain if specific strains are more harmful to horses and other equines.

CLINICAL SIGNS

The clinical manifestations of EPM can range from mild to severe, exhibiting symptoms that affect the brain, brainstem, or spinal cord (20). Initial indications might include with swallowing difficulties, unusual patterns of lameness, or seizures (21). Horses severely affected by the disease may struggle with basic functions such as standing, walking, or swallowing, and the progression of the illness can be rapid. Occasionally, symptoms may briefly improve only to reappear later on. The diversity of symptoms stems from the infestation's impact on various regions of the central nervous system. Typical signs include muscle weakness and instability, often manifesting as stumbling that could be mistaken for lameness. While the condition typically worsens gradually over time, sudden exacerbations leading to recumbency may occur in some cases. Generally, affected horses maintain normal vital signs and appear alert, though some may display signs of thinness and reduced responsiveness. Neurological evaluations commonly reveal weakness, stiffness, and diminished reflexes in the limbs. Key symptoms may encompass decreased alertness, head tilting, facial paralysis, and difficulties with swallowing, although presentations may vary.

DIAGNOSTIC APROACHES

EPM diagnosis confirmation needs post-mortem approach of the animal, especially detection of protozoal infestation in the carcass nervous system. For accurate ante-mortem diagnosis is using: (1) Confirmed typical clinical signs through a neurological exam; (2) Rule out other potential causes, using tools like cervical radiography; (3) Serum test and CSF for intrathecal antibody production against *S. neurona* or *N. hughesi*. Most cases show intrathecal antibodies in the serum to CSF ratio. For uncertain results, use of the Goldman-Witmer coefficient or antigen-specific antibody index. Only the SnSAG2, 4/3 ELISA and NhSAG1 ELISA provide commercial tests for intrathecal antibody production. However, they don't calculate ratios. Commercialy available *S. neurona* and *N. hughesi* IFAT's determine antibody titers in serum and CSF but don't calculate ratios.

POSTMORTEM DIAGNOSIS

Confirmation of EPM in postmortem examination relies on identifying protozoa in CNS lesions, although diagnosis is often presumed even without parasite detection if characteristic inflammatory changes are present. In two reported series, organisms were observed in CNS tissue sections stained with H&E in 10% to 36% of suspected cases. Sensitivity was improved to 20% to 51% through immunohistochemical staining with *S. neurona* specific antibody. While the use of PCR to detect parasites in CNS tissues for postmortem EPM diagnosis hasn't been demonstrated experimentally, it may offer assistance. Notably, the likelihood of histologically finding parasites in tissues from EPM-affected horses treated with antiprotozoal drugs is reduced (22).

IMMUNODIAGNOSTIC TESTING OVERVIEW

There are various tests used for diagnosing EPM, but they're not the main way to diagnose it. Testing for EPM as part of routine health checks or when buying a horse isn't recommended because it's not very reliable unless the horse already shows neurological symptoms. These tests rely on antibodies against the parasites in the blood or spinal fluid detection (23). Antibodies against *N. hughesi* finding in a horse with neurological symptoms is more reliable than antibodies against *S. neurona* confirmation. A negative test usually means the horse hasn't been infected or lives in an area with low parasite exposure. However, a recently infected horse might not show positive results right away, so repeating the test is often needed. Antibody testing of spinal cord fluid is more informative, but it's not always accurate because some antibodies can pass from the blood into the spinal fluid even in healthy horses (24). Using specific tests to measure the amount of antibodies in the spinal fluid can help diagnose active parasite infestation in the central nervous system. These tests have been used in human medicine to diagnose similar infestations, and they've shown good results in diagnosing of EPM in horses too.

AVAILABLE TESTS FOR EPM CAUSED BY *S. NEURONA*

Over the past two decades, several serologic tests have been developed to help diagnose EPM caused by *S. neurona*. These include Western blot (WB), indirect fluorescent antibody test (IFAT), and surface antigen (SAG) enzyme-linked immunosorbent assays (ELISA's) (23, 25). Each test can be performed with serum or CSF, but none of them is considered as perfect variant. The WB, the old fashioned test, looks for antibodies against merozoite lysate but isn't widely used anymore. The IFAT measures antibodies against whole merozoites and can give a ratio of serum to CSF antibodies, but it's not always reliable on its own. The most recent focus has been on SAG and ELISA's, which detect antibodies against specific *S. neurona* surface proteins (26). These last two tests have shown promise in accurately diagnosing EPM, especially when measuring the ratio of antibodies in serum to CSF. While some comparisons between these tests have been made, there's still uncertainty about which one is the best.

DIFFERENTIAL DIAGNOSIS

Nearly all neurological conditions in equines can manifest clinical symptoms similar to those seen in EPM-affected horses. Accurate diagnosis requires a comprehensive neurological examination and diagnostic testing to differentiate

EPM from other potential causes. Some conditions present with distinct signs that help confirm or rule them out. For instance, cervical vertebral stenotic myelopathy (CVSM) typically exhibits symmetricaly located symptoms, with more severe hind limb issues than forelimb problems. Trauma is also a consideration, as it can result in abnormal neurological signs affecting one or multiple limbs. In cases where horses have a history of respiratory disease or abortion outbreaks, EHV-1-associated neurological disease should be considered as a possible alternative. EHV-1-infected horses may develop fever before neurological signs appearing, which usually manifest as symmetric hind limb weakness, bladder problems, and occasionally, tail or hind end issues. Equine motor neuron disease (EMND) is characterized by severe limb weakness and muscle tremors in its early stages, progressing to widespread muscle atrophy in chronic cases. Other potential differentials for spinal cord disease presenting similar clinical signs include various infections, toxins action, metabolic disorders, and structural abnormalities. If cranial nerve or brain involvement is evident, EPM should still be considered as a potential diagnosis. Other differential diagnosis include viral infections, tumors, trauma, and metabolic disorders.

TREATMENT AND PREVENTION

For therapy of EPM, using one of the FDA-approved anticoccidial drugs is recommended. These include Ponazuril (Marquis®), Diclazuril (Protazil®), and Sulfadiazine/ Pyrimethamine combination (ReBalance®). Additional causal and supportive treatments should be provided focused on the severity of neurological deficits.

The combination of Sulfadiazine and Pyrimethamine was one of the initial treatments for EPM, working by interfering with folic acid metabolism necessary for the parasite's survival. However, there are potential side effects, including bone marrow suppression and gastrointestinal issues (27). Pyrimethamine can also cause birth defects in animals and should not be used in pregnant mares. Despite the potential risks, these drugs have shown success in treating EPM in 60-70% of all clinically manifested cases.

Diclazuril and Ponazuril are two FDA-approved drugs for treating EPM. They belong to the benzeneacetonitrile group and are thought to target the parasite's apicoplast organelle (28). These drugs have shown broad-spectrum activity against various protozoa species and have been proven effective in horses. Pharmacokinetic studies have shown that therapeutic levels of these drugs are reached within few days of treatment (29). Ponazuril can be administered with vegetable oil to increase its effectiveness, while Diclazuril doesn't require a loading dose or oil. Treatment with these drugs typically lasts for 6-8 weeks or longer, depending on the horse's organism response to the trerapy. Nonsteroidal anti-inflammatory drugs like Flunixin meglumine are often given alongside antiprotozoal treatment to manage thevsymptoms. In severe cases, corticosteroids and Dimethyl sulfoxide may be used to control inflammation. Additionally, vitamin E is sometimes used as an antioxidant, although its effectiveness is still being studied.

Prevention of EPM involves measures like reducing stress and minimizing exposure to opossum feces. Practical steps like feeding horses off the ground, providing separate water sources, and keeping wildlife away from horse farms can help for prophylaxis. Using coccidiostatic and coccidiocidal drugs intermittently is another preventive strategy (30). Studies have shown that applying ponazuril before exposure to the parasite can reduce symptoms and delay disease. Similarly, giving low-dose diclazuril to horses can reduce the risk of infestation (31). These preventive measures show effectiveness but need further research to establish standard preventive protocol.

CONCLUSIONS

In equines showing clinical signs of EPM, a thorough neurologic examination is crucial to identify deficits and find out the cause of disease. Testing serum and CSF for specific antibodies can confirm EPM and rule out other potential neurological disorders. Treatment involves FDA-approved drugs along with supportive therapy and the intercourse duration depends on symptoms improvement. Reassessment is necessary if symptoms reocur. More information about these parasites and the knowledge of equine immune response to them, better diagnostic procedures, treatment protocols, and preventive measures will lead to early detection and eradication of this severe and sometimes fatal protozoa caused parasitic disease.

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