# "How Stella Got Her Groove Back"

## Equine Protozoal Myeloencephalitis

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**Introduction:**

The following case report will highlight a neurologic disease commonly found in horses with no breed predisposition. It is the most common diagnosis in horses presenting with neurological disease in the United States. Less than 17,000 horses are actually cured and relapses occur commonly [4,10]. While any age of horse may become affected by equine protozoal myeloencephalitis, horses greater than 13 years of age are documented to be at a greater risk. Additionally, there have been reports documenting increased incidence in horses less than 4 years of age. Equine protozoal myeloencephalitis (EPM) has many presentations and presenting as ataxia, lameness, or stumbling. Some horses may show abnormal behavioral changes, have trouble eating (dysphagia), exhibit abnormal airway functions, or even present with seizures. Clinical signs are typically due to inflammation as part of the disease syndrome rather than actually being an active protozoal infection.

This case report will review the pathophysiology, life cycle of the protozoa, clinical signs, diagnostics, treatment, and prognosis of the disease as well as the outcome of the patient, "French Discos Blonde" or by her barn name of "Stella", who was seen by the medicine department of the Equine Department at Mississippi State University, College of Veterinary Medicine.

**History and Presentation**

Prior relevant history of French Discos Blonde (with her barn name known as "Stella") began when she was a 14 year old barrel racing quarter horse mare who originally started showing neurological deficits on April 25$^{th}$, 2019 in her stall at a barrel racing event. Her referring veterinarian started administration of dimethyl sulfoxide (DMSO) and began treatment

for EPM with Diclazuril April 26th until May 1st and was then started on levamisole and Decoquinate orally accompanied by Rebalance and Marquis. On presentation according to her referring DVM Stella had suspected blindness, inability to blink, and proprioceptive deficits. She was evaluated by an ophthalmologist who was able to determine that her globe was normal and the eye itself did not appear to be the cause of her vision loss. Stella presented to MSU CVM Equine Service on May 6th 2019 for vision alteration and persistent neurological disease. Upon presentation to MSU CVM, Stella was given a complete neuro exam which showed her to be improving since her last exam with her referring DVM since starting the treatment for EPM. Stella was once again rechecked on May 30th 2019 at MSU CVM where she was deemed to have a normal neurological status. She was given an excellent prognosis for return to previous performance level and to maintain her current medications of Vitamin E, Rebalance, and Equioxx until they ran out.

History of current problem: Most recently Stella presented to MSU CVM at 16 years old on March 18th 2021 for neurological deficits. On March 13th 2021, Stella performed in a barrel race and between her 1st and 2nd barrels, the owners noted that she tossed her head and faltered in her gait. When coming around the second barrel she slid and fell into lateral recumbency. It was noted that she rose immediately and no evidence of head or neck trauma. On March 15th 2021, the owner observed that Stella was dropping food while trying to eat, had a twisted nose/ drooping lip, inability to blink her left eye, had apparent left eye blindness, had a small amount of opaque discharge coming from her left eye with a slightly drooping left ear as well.

Upon presentation her physical exam parameters were within normal limits and she was bright, alert, and responsive. She weighed 939 lbs, had a temperature of 100.0 F, pulse rate of 60 bpm, respiratory rate of 20 brpm, and a body condition score of 5/9, although her owners stated

she had recently lost weight. Her face was asymmetrical, her nose and upper lip deviated towards the right with a flaccid/ drooping lower lip and left ear. She had symmetrical eye position, however, her left eye was dry with a large exposure ulcer covering the center of her eye.

**Diagnostics**

An initial CBC large animal profile with fibrin and a large animal chemistry profile had no significant findings other than mild elevations in CK (creatinine kinase) and AST (Aspartate aminotransferase) which are both muscle enzymes that can elevate when there is a significant amount of muscle damage or strenuous exercise. In her case, these elevations were likely due to her recent barrel event that took place on 3/13/2021 and her trailer ride to the school which are not related to her neurological deficits. A gait assessment score can be used and gives the horse a numerical value that is between 0 to 5. A full cranial nerve neurological exam with the following results: CN I (olfactory) appeared normal and intact. CN II (optic) appeared normal and intact with an intact PLR. Her left vision was reduced but still apparent. She had no menace response present. CN III (oculomotor): She had normal eye position and pupillary light responses and was deemed to be intact and normal. CN IV (trochlear): She had normal eye position and was deemed to be intact and normal. CN V (trigeminal): She had an absent left corneal reflex and had no reaction to corneal touching. This nerve was deemed to be abnormal. CN VI (abducens): There was no left retractor bulbi reflex to corneal touch or menace, however, the eye position was normal so the dysfunction for CN VI may be due to dysfunction found in V and VII. CN VII (facial): She was found to have no left palpebral reflex, inability to blink, a drooping ear but still able to have some mobility, nose and upper lip deviation to the right, and decreased tear production causing dry eye. Due to all these abnormalities her CN VII function was deemed to be abnormal. CN VIII (vestibulocochlear): There was suspicion of mild

vestibular signs on arrival \, but it was difficult to assess. There was no head tilt/ turn or circling. *She developed true vestibular signs after EPM treatment was started which can be due to inflammation causing more clinical signs*. This nerve was determined to be abnormal as well. CN IX (glossopharyngeal): No roaring sounds were appreciated and deemed to be a normal intact nerve. CN X (vagus): was deemed normal due to no roaring breath sounds. CN XI (accessory): No shoulder muscle atrophy or asymmetry was noted and it was deemed to be normal and intact. CNXII (hypoglossal): She had normal tongue position and tone and was able to swallow normally so this nerve was deemed to be normal and intact. With EPM the most common manifestations seen are asymmetric vestibular (VIII) nerve dysfunction. We will also commonly see facial paralysis (VII), signs of dysphagia (IX, X), laryngeal paralysis (X), tongue paralysis (XII), strabismus (III, IV, VI), weak jaw tone (V), and corneal areflexia (VI)[8]. After a gait analysis/ full neurologic exam, the next best diagnostic step is to collect serum and CSF fluid.

On 3/19/2021, due to her clinical presentation and past history of EPM, the decision was made to submit samples for a CSF analysis and a *Sarcocystis neurona* and *Neospora hughesi* ELISA ratio test. It is important to note that there are actually no test that are licensed through the USDA as "EPM" diagnostic tests. The presence of antibodies does not actually detect disease, however seeing antibodies against *S. neurona* along with seeing the certain clinical signs or presentation are a greatly supportive diagnosis of EPM. A true diagnosis is made on a post-mortem exam. There are several antibody tests that can be performed that are pathogen specific. Stella specifically had the combined SAG 2,3,4 serum to CSF titer ratio test. Surface antigens glycoproteins 2,3,4 are the newest surface antigens used to test for EPM[3,6,8]. While it is possible to send in separate serum and CSF samples, it is best to send in, the ratio of serum: CSF titers

which is very predictive for an EPM diagnosis[3]. As the intrathecal IgG production increases, the titer ratio between CSF and serum will decrease. Ratios that show to be <100 can strongly suggest that the patient has an active case of EPM.

The serum and CSF were obtained and the ratio for a combined SAG 2,3,4 titer on serum was a 1:1000[8]. The interpretation of this specific ratio is a positive serum detection of those specific antibodies. This implies that the patient was exposed to *S. neurona* but does not confirm clinical disease alone. A negative ratio is classified as a titer <1:250 and a high titer is classified as a ratio >1:4000. The test results for the combined SAG 2,3,4 CSF titer ratio was 1:20. This also classified as a positive titer result. A negative titer ratio for this test is <1:2.5 and a high titer at a ratio of >1:40. A CSF titer of a ratio >/- 1:20 indicates an active disease caused by *S. neurona*. Since a serum and CSF sample were both sent in the lab was able to do a serum to CSF titer ratio. This ratio was 50. A serum CSF titer ratio of <100 is highly diagnostic of clinical EPM. A titer of less than 100 is indicative of intrathecal antibody production. A serum and CSF sample was ran to detect *Neospora hughesi* antibodies, however all the ratios for this specific protozoan both came back low, indicating that no antibodies were detected for *N. hughesi* in the serum or CSF. After all diagnostic testing it was concluded that the cause of Stella's neurologic signs were due to a relapse of her previous EPM infection. EPM is typically diagnosed by physical and neurological examination and the diagnosis can then be supported with ancillary testing to support the etiology, like in Stella's case[3,6].

**Pathophysiology**

The first step to understanding EPM in horses is to start with understanding the life cycle of the actual causative agent of the infection. There are two different protozoa that cause EPM in horses. One species is the *Sarcocystis neurona* and the other is *Neospora hughesi.* Horses can be infected with either, however, *S. neurona* is the more causative agent and the important part is where this protozoa ultimately ends up. If a horse is infected with *Sarcocystis* the infection is simply called a sarcocystosis and is usually only confined to the gut and in the muscle[1]. The *Sarcocystis spp* belongs to the phylum Apicomplexa which takes advantage of an obligatory predator-prey life cycle typically with a narrow host range[1,2]. The protozoa will live in a definitive host, which in this case is the opossum. The definitive host will release infective sporocysts, which are the eggs that have ruptured called sporulated oocysts typically before they leave the GI tract that are shed from the gut wall into the environment through their opossum host. The sporocyst are then shed into the environment and introduced into food and water supply of the prey of intermediate host. Once in the environment the sporocysts can be ingested by an intermediate host, such as a birds, cats, skunks, raccoons, or a number of other small mammals. Once inside of the intermediate host, the sporocyst will excyst and then enter the cells of the skeletal muscle where they will develop into sarcocysts. The life cycle will then come full circle when the definitive host ingests the sarcocysts that are lodged in the muscle cells of the intermediate host. So the question is how does the horse fit into this predator-prey life cycle if it's not eating prey or being eaten by a predator? Sarcocysts can have host called aberrant, or sometimes referred to as a dead-end host. They are referred to as aberrant because only the meront and schizont stages of the life cycle are found in the horse and not the final adult forms. The host can ingest the sporocysts that contaminates the food or water sources when they are shed from the GI tract of the definitive host, the opossum. Through this fecal-oral contamination,

the sporozoites penetrate intestinal epithelium and travel to somatic tissues by the way of blood vessels, although the exact route they take from ingestion to CNS is not clearly understood yet[2,5]. They will produce asexually in these somatic tissues into merozoites and then travel to the brain and spinal cord. The merozoites will infect neural cells (i.e. neurons, mononuclear cells, glial cells) in the CNS (brain and spinal cord)[2,5,6]. The development of these schizonts can cause pressure to be put on surrounding nervous tissue causing these neural cells to die and then the merozoites will be released into the CNS and CSF. Horses can be infected with another species of sarcocystis called *Sarcocystis fayeri* in which they are the natural host, however, this species causes a different set of clinical signs. With this species the sarcocystosis is called equine muscular sarcocystosis (EMS), which can cause neuromuscular signs where toxins are released from degrading sarcocysts and is a more common infection than *S. neurona*. *S neurona* infections have associations with CNS inflammation while *S. fayeri* sarcocysts do not elicit such an inflammatory response.

**Treatment**

Once a diagnosis of EPM can be made, treatment should start immediately to help slow the signs of neurological disease. Delaying in treatment leaves potential to cause more permanent damage to the central nervous system. There are three primary treatments used for EPM: the first is a sulfadiazine/ pyrimethamine (ReBalance) which can cause a blockade of folate metabolism in protozoa, which will in turn eliminate its ability to reproduce. This drug must be given for 3 - 7 months in order to limit reproduction long enough[7,9]. Precaution should be taken with this drug as it can cause bone marrow suppression and anemia so bloodwork should be monitored throughout the use of this drug.

Diclazuril (Protazil) is an FDA approved drug that is based on a herbicide that attacks the chloroplast function of the protozoa. It is considered to be non-toxic at higher doses to other mammals and has no reportable side effects. This drug is labeled at 1 mg/kg while it is commonly compounded at 5-15 mg/kg dosages. In treating relapse cases it can be used at a 7 mg/kg body weight dose, however, it is not an FDA approved protocol and has no efficacy studies[7,9].

Ponazuril (Marquis) is an anti-protozoal drug believed to target protozoal organelle. It is in the same drug class as Diclazuril so it as well is based off a herbicide that attacks chloroplasts function of protozoa. You can see minor side effects such as rash and mouth blisters. It is labeled at 5 mg/kg body weight and is given once for up to 28 days. In treating relapse cases this drug can be used at 35 mg/kg body weight for the first four days then 5 mg/kg for 28 days, although that protocol is not FDA approved and has no efficacy studies. It is important to note that a successful EPM treatment does not 100% eliminate all protozoa, but eliminates enough for the host own immune system to take control and kill off the rest[7,9].

Adjunctive therapies used in EPM treatment are not limited to but include non-steroidals, steroids, DMSO, vitamin E, levamisole along with supportive care. Vitamin E is a highly encouraged supplementation due to its properties of being a potent antioxidant that can help support nerve function and as well as the immune system. It is also important to provide a healthy balanced diet that supports the horses needs of the proper vitamins, minerals, and amino acids. NSAID's such as phenylbutazone or banamine are used in horses that show moderate to severe signs during the first week of treatment for EPM to help combat worsening of the neurological deficits and any extra inflammation that may be caused during the death of the protozoans[9]. A short course of steroids or DMSO is warranted in patients that show brain

involvement or pose a danger to themselves by falling to also help reduce an inflammatory response. Treatment length of the FDA approved antiprotozoals usually last around 1 month, however, can exceed from 3-9 months depending on clinical improvement[9].

**Prognosis/ Prevention**

If EPM is left undiagnosed and untreated, it can cause lasting damage to the central nervous system. There is a high success rate in cases of treated horses, however, there is a 10-20% chance of relapsing within 2 years of previous treatment[9,10]. With relapse cases, a prompt diagnosis should be made and re-treatment should be started immediately.

In order to have a successful prevention of EPM it is important to understand where they are getting the infection from. The most common presumed way that horses pick up sporocysts is from contaminated food and water sources by way of opossums. Opossums are omnivores meaning they eat food of both plant and animal origins and are attracted to moist or dry cat/ dog foods, grains, fruit, and garbage. It is best to not leave horse or pet feed out in open bags and garbage should be kept away in metal containers that cannot be broken into. It is also advisable to not have bird feeders or fallen fruit from trees that can attract birds or opossums around where your horses may graze. It is also practical to keep herding dogs around that can protect/ scare off opossums. also It can be beneficial to have paddocks opossum proofed by placing a partially buried mesh fence that is about 2in x 4 in with electric wiring on the outside of a horse fence that already exist. Contaminated feed containers can be steam cleaned. Steaming has been proved to kill sporocysts[9].

**Case Outcome**

After diagnostics were taken on Stella and upon waiting for the results of her CSF/ serum ratio test, she was started on a list of precautionary medications. The cranial nerve deficits leading to her inability to blink ultimately caused a superficial corneal ulcer in which she was given a sub palpebral lavage system and a temporary tarsorrhaphy to protect her eye from the environment. Her first day in hospital she was started on banamine at 1.1 mg/kg IV to control inflammation that occurred secondary to the EPM and treatment, as well as pain that could be associated with the ulcer in her left eye. She received DMSO 10% solution in LRS as a 1-liter bolus IV once a day for 4 days. She received vitamin E 400 IU orally every 24 hours, and a number of eye medications to treat her ulcerated eye. While awaiting results for the CSF/ serum ratio she was started on Marquis (Ponazuril). After the results were received, the treatment of Ponazuril was continued and ReBalance (Sulfadiazine/pyrimethamine) was also started. While undergoing her initial treatment, Stella's clinical signs and ataxia appeared to worsen, which is called a "treatment crisis" due to the rapid death of the protozoal organisms followed by inflammation around the nerves. She was administered steroids to help combat this inflammatory flare-up but they were used sparingly due to the fact that they can inhibit the natural inflammatory and healing process of her own defense system. Stella's neurological signs eventually began to improve around her 8$^{th}$ day out of a total of 15 days in hospital (discharged 4/3/2021). She received ophthalmic medications daily through the sub palpebral lavage system in hospital and the tarsorrhaphy was removed on 4/8/2021 by the ophthalmologic department. She will continue to undergo 6 week rechecks to have blood drawn while undergoing treatment to monitor liver and kidney values. Her neurological signs continued to be improving since her day of discharge and will keep seeing the ophthalmologic department to check the progress of her left superficial corneal ulcer. Stella is successfully on her way to getting her groove back.

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