A Whole Neurologic World

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Class of 2019

Clinicopathologic Conference

November 9, 2018

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Introduction:

Seizures are a common medical ailment of many species, including humans and dogs, with a wide variety of underlying etiologies from neurologic to metabolic to idiopathic. While a significant amount of effort is devoted to seizure control in other areas of veterinary medicine, this is not true of equine care, as the frequency of seizure activity in horses is comparatively less common to that of other species. This could be due to the relatively high seizure threshold of the equine species, but it is also likely due, at least in part, to the wide variety and ambiguity of terms used by equine practitioners.[1] Seizures have a range of clinical manifestations, sometimes affecting only focal muscle groups and sometimes being more generalized and affecting all motor activity. They can also be simple, allowing an animal to display normal consciousness, or complex with impaired awareness. Due to the array of signs from focal muscle fasciculations to recumbency, it is sometimes difficult to ascertain whether a true seizure event has occurred. A thorough investigation into the history of the seizure episode as well as the animal, itself, can give clues as to the true nature of the event as well as possible precipitating factors.[1] The ultimate goal is to determine the etiology of the seizure, if there is one, to facilitate treatment and prevention of future episodes.

History and Presentation:

Jamil is an approximately 10-year-old Arabian stallion that presented to the Mississippi State University College of Veterinary Medicine (MSU CVM) Equine Medicine Service as an emergency on February 21, 2018 for seizures of approximately 24 hours duration. There were no changes in his lifestyle or behavior in the preceding weeks. He was also appropriately vaccinated with all core vaccines recommended by the American Association of Equine Practitioners,

though boosters were due to be administered at the end of February. On the morning of February 21, 2018, Jamil was approached by his owner and acutely rolled over backwards, thrashing violently with generalized muscle spasms. This continued for approximately two minutes before he settled down and regained his footing. Approximately three to four similar episodes, presumptively seizure-activity, occurred later that morning and into the afternoon. Until the first episode, the owners had noticed no abnormal mentation and no changes in the patient's appetite. Upon presentation to the MSU CVM, the patient was quiet, alert, and responsive with a moderate tachycardia of 60 beats per minute. Thoracic auscultation was unremarkable with normal lung sounds and no cardiac murmurs or arrhythmias evident. Gastrointestinal motility was appropriate in all four quadrants. Numerous superficial skin abrasions were present, primarily on the face, shoulders, and distal extremities, with mild to moderate swelling of the right hindlimb. Neurological examination revealed normal cranial nerve function with a quiet mentation, possibly indicative of a post-ictal state. The patient displayed a base-wide gait and ataxia, though complete gait evaluation was not performed to prevent further injury to Jamil. Without a full gait analysis, it is difficult to localize where the insult is affecting the nervous system. In this case, however, the history of seizures specifically allows for localization of a cerebral lesion. The rest of the physical exam was within normal limits.

The patient was immediately placed in a padded stall and administered one hundred milligrams diazepam intravenously, though he was not actively seizing. Jamil subsequently experienced a dysphoric episode, characterized by falling and thrashing for approximately four minutes. After allowing the patient to relax, a jugular catheter was placed and one pint of dimethyl sulfoxide (DMSO) in five liters Lactated Ringer's Solution with five hundred milliliters magnesium sulfate was administered over one hour. Phenobarbital therapy was initiated on the

evening of presentation in an effort to control seizure activity and silver sulfadiazine was applied topically to the superficial abrasions. DMSO was selected as an anti-inflammatory agent in this case as it is useful when administered intravenously as a method to reduce cerebral edema. Magnesium is a membrane stabilizing electrolyte that binds to the calcium channels of neurons and was used to control seizure activity by inhibiting excessive neuronal firing.

A complete blood count showed no significant abnormalities while a serum chemistry revealed a mildly elevated creatinine at 1.94 mg/dl (reference range: 1.2-1.9), a mildly elevated globulin at 4.3 g/dl (reference range: 2.5-4.0), a mild hypophosphatemia – 2.3 mg/dl (reference range: 2.4-4.0), a moderate hypomagnesemia – 1.3 (reference range: 1.6-2.5), and a markedly elevated CK – 1864 (reference range: 57-283). Blood lactate measured 1.6 mmol/L. A blood sample was also collected to send out for neurologic disease testing at UC Davis. Cerebrospinal fluid would have been an ideal sample addition, but collection would have posed a major challenge while also being extremely dangerous for both Jamil and those performing the procedure. Initial rule-outs for the patient included Eastern Equine Encephalitis (EEE), West Nile Virus (WNV), Equine Protozoal Myeloencephalitis (EPM), Temporohyoid Osteoarthropathy (THO), and traumatic basisphenoid or basioccipital fracture.

While awaiting the results of the send-out tests to rule out WNV, EEE, and EPM, the patient was maintained on a daily phenobarbital regimen for seizure control. Serum phenobarbital levels were monitored serially throughout the hospital stay to ensure they were within the reference range of 15-45mcg/ml. Radiography was performed to determine the likelihood of THO or existing skull fractures. During sedation with diazepam for this procedure, another short dysphoric event occurred with the patient exhibiting severe ataxia, falling, and thrashing. Only minor superficial abrasions were sustained during this event and the patient subsequently became

sedate, allowing for radiographs to be obtained. The images showed a possible abnormality of the stylohyoid bones bilaterally but no other obvious fractures or abnormalities of the skull. After allowing the patient a day to recover from sedation for radiographs, an upper airway endoscopy was successfully performed without chemical restraint. An abnormality of the right stylohyoid bone was identified in the right guttural pouch and was suspected to be a healed fracture from a previous injury. No other abnormalities were noted in either pouch and there was no evidence of THO. At that time, the remaining rule-outs were all dependent upon the send-out neurologic tests.

Test results were negative for Eastern Equine Encephalitis and West Nile Virus. There was also a negative result for the presence of antibodies to *Neospora hughesi*, which is one of the etiologic agents of EPM. The major organism associated with EPM is *Sarcocystis neurona*, to which this patient had a markedly high titer of 2650. Any result greater than or equal to 650 indicates a 96% probability of Equine Protozoal Myeloencephalitis due to *S neurona*.

Pathophysiology:

EPM is most often caused by *Sarcocystis neurona* with *Neospora hughesi* being diagnosed less frequently. One 2017 study indicates that *Toxoplasma gondii* may play a role in the development of EPM, as well.[2] *S neurona* organisms are transmitted through the feces of their definitive host, the opossum *Didelphis virginiana.* Other rodent-like animals can also carry the pathogens, such as raccoons, skunks, armadillos, and cats. Birds serve as the intermediate host and help to spread the protozoa geographically. The life cycle is completed when birds carrying the organisms are scavenged by other birds or rodents. Horses are a dead-end host that are infected when a definitive host defecates in an area where it may contaminate a horse's feed

or water. Horses then ingest the contaminated water or feed material. While every horse is considered susceptible to EPM, not all horses infected with *S neurona* or *N hughesi* will develop clinical disease.[3] Many horses can withstand this exposure and their immune systems prevent serious infection. Horses that lack the ability to fight off infection will then develop clinical illness, but it is unclear exactly what causes a progression to severe neurologic disease.[3] According to a 2017 study, 85% of tested horses in the South region were positive for antibodies against *S neurona* in serum, the highest percentage of all areas within the United States.[4]

It is most common that horses will present with progressive and asymmetric neurologic deficits, though no signs are considered pathognomonic.[5] This information can allow a decreased suspicion of EPM when an animal presents with neurologic deficits that are symmetric. Any area of the central nervous system can be infected, leading to a wide array of acute to chronic signs, often with an insidious onset. Infection and disease of the gray matter results in focal muscle atrophy, commonly of the gluteal region, and severe muscle weakness. Affected white matter will cause ataxia and weakness of the limbs caudal to the infected site. Depression, difficulty swallowing, abnormal mentation, cranial nerve paralysis, gait abnormalities, head tilt, and even seizures are signs that may be seen in a patient with EPM, though these occur far less often than those previously mentioned. It is not uncommon for early indications of EPM to be mistaken for lameness or simply poor performance in working horses. EPM seldomly affects more than one horse on a single farm, though clusters of cases can occur. Most cases, according to post-mortem data collected from diagnostic centers in the U.S.A. and Canada, have occurred in horses less than 5 years old.[3] It has also been reported that EPM more commonly affects young horses 5 years of age and less as well as horses older than 13.[3]

Definitive diagnosis of EPM requires post-mortem detection of *S neurona* or *N hughesi* organisms within the central nervous system. There are commercially available tests that can be performed using serum and cerebrospinal fluid (CSF) from EPM suspects that rely on the detection of intrathecally produced antibodies against one or both etiologic agents leading to EPM in the CSF.[6] These tests include Western blot, indirect fluorescent antibody testing (IFAT), and *S neurona* surface antigen enzyme-linked immunosorbent assay (SnSAG ELISA). One of the most common tests is IFAT, run by the University of California - Davis. While many people desire a simple test that can be run solely on serum because of the ease of collection, this has minimal diagnostic value to support a diagnosis of EPM as a stand-alone diagnostic and has been shown to have low agreement with disease status.[6] Markedly elevated serum titers do have correlation with disease when neurologic signs are present, though the optimal tests available are IFAT run on CSF and SnSAG ELISA serum to CSF titer ratios.[6] Equine protozoal myeloencephalitis is ultimately a diagnosis of exclusion and the recommendations for reaching that diagnosis include 3 steps:

1) Performing a thorough neurologic examination revealing neurologic deficits consistent with EPM,
2) Ruling out other neurologic disorders causing similar signs,
3) Testing serum and CSF to detect specific antibodies to *Sarcocystis neurona* or *Neospora hughesi.*[5]

It is also important to note that serology performed as a part of general health screening on horses with no other cause to be suspected for EPM has a low positive predictive value. [3]

Treatment is aimed at eradication of the infecting organism while minimizing inflammation, both from initial infection as well as that created with successful treatment and

dying protozoal organisms within the central nervous system. Currently, there are three methods of treatment for EPM that are approved by the US Food and Drug Administration (FDA). Historically, the treatment of choice for EPM was pyrimethamine with sulfadiazine, now marketed as a drug with the trade name Rebalance. Both chemicals in this formulation inhibit folate synthesis and, thereby, prevent the production of purine and pyrimidine nucleotides for nucleic acid synthesis.[5] Side effects of pyrimethamine sulfa are related to inhibition of folate synthesis in the horse and include diarrhea, bone marrow suppression, urticaria, and anorexia. Treatment with this method is long, extending to six months, and the short half-lives of the component drugs result in large fluctuations between peak and trough serum values. Pyrimethamine is also considered teratogenic and it is contraindicated for use in pregnant mares.[5] The two other drugs approved for EPM treatment are both benzeneacetonitrile agents: diclazuril as Protazil oral pellets and ponazuril as Marquis oral paste. Both drugs are anti-protozoal with little to no toxicity expected at therapeutic doses. Side effects are rare but may include diarrhea, anorexia, weight loss, mild colic, blisters of the mouth and nose, skin rash, and hives. These drugs have long half-lives and can take up to seven days to reach steady-state concentration levels in blood so a loading dose three times that of the normal dose of 5mg/kg is often administered on the first day of therapy with ponazuril while watching carefully for any of the aforementioned negative effects. Bioavailability of this specific product can also be increased up to fifteen percent by the administration of vegetable oil.[3] Treatment duration with either of the benzenacetonitrile agents is labeled for 28 days, though it is recommended that cessation of treatment be based upon neurologic improvement with true treatment success being strictly defined as improvement of at least one clinical grade on neurologic examination and a negative *S neurona* antibody status in the CSF.[3,5] Other treatment modalities and adjunct therapies exist for

EPM that are not FDA approved. These include biologic response modifiers and other anti-apicomplexan drugs, sometimes used in conjunction with FDA approved therapeutics.[3, 5] The addition of flunixin meglumine for the first three to seven days of treatment will help to control inflammation and occasionally a corticosteroid may be added to treatment for not more than three days in animals with severe neurologic signs or that are recumbent.[5] The damaged central nervous system is also subject to oxidant injury and antioxidant treatment with Dimethyl sulfoxide or vitamin E supplements can be added as an adjunct in anti-inflammatory therapy.[3]

Prevention of EPM centers around decreasing stress in horses as well as reducing their exposure to feces from opossums. Intermittent treatment with coccidiostatic or coccidiocidal drugs has been shown to be an effective method at minimizing but not eliminating infection in horses.[3] This preventive modality requires more research to create a standard protocol, though there is good potential for its use in reducing EPM incidence in high-risk horses.[5] Practical approaches of prevention include feeding horses off the ground as well as preventing wildlife access to horse feed, water, and confinement areas. Effective methods of preventing infection will reduce the costly financial burden on horse owners while also greatly decreasing disease morbidity in equine patients.

Treatment and Management:

Jamil was definitively diagnosed with Equine Protozoal Myeloencephalitis and treatment for this condition was initiated immediately. While hospitalized, the patient received 30mg/kg Trimethoprim Sulfa (TMS) orally every 12 hours for treatment of infectious causes of seizure activity prior to definitive diagnosis, 5mg/kg Ponazuril orally once every 24 hours specifically for treatment of Sarcocystis neurona infection, Phenobarbital orally titrated to a trough level

within the established safe reference range for seizure control, 3ml of a vitamin E supplement orally once every 24 hours to combat oxidant injury of the central nervous system, 1.1mg/kg flunixin meglumine intravenously every 12 hours for inflammation, 5mg/kg methylprednisolone sodium succinate intravenously once at presentation with a second dose 12 hours later for severe inflammation on presentation, and 0.1mg/kg Dexamethasone SP intravenously once on February 22 and a second dose 12 hours later also for the initial severe inflammation. Jamil was maintained in a padded stall with decreased light and notifications for traffic in the surrounding area to choose an alternate route and maintain a low volume.

The patient exhibited signs of dysphoria on more than one occasion in the hospital after receiving diazepam intravenously, a known side effect of the drug when used as a sole agent, but no true seizure activity was noted during his stay. Blood phenobarbital levels were scrutinized throughout the duration of the patient's time in the animal hospital and the dosing interval was adjusted accordingly with the recommended reference range of 15 to 45mcg/ml for the control of seizures. Other options for prevention of seizure activity include potassium bromide and phenytoin. At the time of discharge, he was maintaining appropriate systemic phenobarbital concentrations at 8 mg/kg dosed every 12 hours.

Upon discharge of the patient, the owners were advised that Jamil be confined to a stall or paddock to prevent injury to other horses or humans while continuing treatment at home. He would be monitored for seizure activity, abnormal behavior, and improvement in his ataxia until returning to the MSU CVM for follow-up examination and testing of serum for phenobarbital concentration as well as titers to *S neurona*. The patient was sent home with phenobarbital dosed at 8mg/kg every 12 hours orally, ponazuril dosed at 5mg/kg every 24 hours orally, and firocoxib (Equioxx) dosed at 1 tablet once every 2 hours orally for inflammation. It was explained to the

owners the importance that phenobarbital be given at the correct dosing interval and that no doses be missed as this could induce a seizure. Administration of the drug should be tapered slowly over time to lessen the likelihood of inducing a seizure. A plan for tapering Jamil's phenobarbital dosing would be created once EPM treatment was completed with seizure activity controlled.

Case Outcome:

The patient returned to the MSU-CVM for serial serum phenobarbital as well as IFAT titer testing over the next several months. Serum phenobarbital levels were tapered to 7.5mcg/ml on May 3 and the drug was subsequently discontinued as no further seizure activity had been noted since discharge and there was difficulty acquiring a sufficient for such a large animal from pharmacies. Testing for *Neospora hughesi* was consistently negative on follow-up visits while *Sarcocystis neurona* titers showed a downward trend with test results of 640 on May 3 and 160 on June 25. All medications were discontinued prior to June 25 at which time it was determined that no further follow-up blood tests were needed. Jamil is currently doing well with no neurologic deficits and, according to the owners, is back to his normal self.

References:

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