

As provided by Ms. Rachel Kipp (2008)

“Missy” is a 6 year old quarter horse mare who presented to the Veterinary Medical Teaching Hospital (VMTH) on November 10, 2007 with an acute onset of neurologic symptoms. She arrived anxious and recumbent in the trailer and was thrashing while making unsuccessful attempts to stand. The VMTH staff members were able to enter the trailer just long enough to collect blood and sedate Missy with 5 milligrams (mg) of butorphanol and 5 mg of detomidine. This dose allowed VMTH staff to place a 14 gauge IV catheter into the right jugular vein and keep the anxious mare quiet until the anesthesia department arrived to assist in removing the fractious mare from the trailer.

HISTORY

The owner provided us with the history of her mare while VMTH hospital staff waited for the arrival of the anesthesia department. We learned that Missy was a performance barrel racing quarter horse that was purchased and transported from Canada on Easter weekend earlier this year. At the time of transport, she was given all vaccinations necessary (including Rabies) to cross the Canadian/United States border. She arrived at the VMTH on November 10, 2007 with a current vaccination status for Rabies, West Nile Virus, Eastern and Western Encephalitic Viruses, Tetanus, Influenza, and Rhinopneumonitis. We were told that Missy spends most of her time on pasture with other horses and that she had been acting quiet and withdrawn from her herdmates for the last couple days. On the morning of November 10, 2007, Missy was found down in the pasture, drooling from the mouth and unable to rise. The owner initially believed her mare to be colicky and administered a 1000 pound dose of oral flunixin to help relieve pain. The owner was able to get the mare to a standing position and walk her onto the trailer with great difficulty. The owner also reported that Missy’s appetite had been decreased earlier that

morning and that she appeared to be having difficulty urinating. She was reported to posture but produce only a small volume of urine. Missy normally eats a diet consisting of mixed grass and alfalfa hay, 4 cups of a performance feed and a probiotic. When asked, the owner replied that none of the other horses appeared to have signs of respiratory illness.

PATIENT STATUS

When the anesthesia department arrived, they formulated a plan for anesthesia that would allow safe transport of the mare from the trailer into a padded stall equipped with a sling. Using an estimated weight of 450 kilograms (kg), a 200 mg dose of xylazine was administered, followed by 50 mg of ketamine and 1 gram (g) of diazepam for induction of anesthesia. A “triple drip” infusion consisting of 1000 milliliters (ml) of 5% guaifenesin, 1000 mg of ketamine, and 500 mg of xylazine was administered to maintain anesthesia. Because this method of intravenous anesthesia (IVA) produced good muscle relaxation and anesthesia, Missy was able to be safely transported to the semi-isolation stall where she was placed in a sling. An atlanto-occipital spinal tap was performed, yielding markedly xanthochromic cerebral spinal fluid (CSF). The horse was recovered uneventfully in the sling. Shortly after, aseptic technique was employed to evacuate the bladder with a stallion catheter. Evidence of a full bladder supported the owner’s observation given in the history. Once fully recovered from the effects of the IVA, a physical exam was performed, followed by a more sterile catheter placement with a 14 gauge long term over-the-wire catheter in her left jugular vein.

Physical examination of the alert and responsive mare in the sling revealed a temperature of 100.0 F, heart rate of 36 beats per minute, and a respiratory rate of 24 breaths per minute. Her mucous membranes were pink, with a capillary refill time (CRT) less than 2 seconds. Gut

sounds were ausculted in all 4 quadrants and digital pulses were within normal limits. Bladder and rectum had been evacuated manually prior to the physical exam. A formal neurologic examination could not be performed since the mare arrived down in the trailer, but cranial nerve deficits were absent and the mare was of normal mentation during her initial physical exam in the sling. It is likely that the gross appearance of the CSF combined with the bladder paresis, recumbency, and acute onset of symptoms led the VMTH doctors and staff to a strong differential diagnosis of Equine Herpes Virus Type 1 (EHV-1). With aggressive therapy, the client was informed that improvement within the first 24 to 48 hours would best determine prognosis.

INITIAL DIAGNOSTICS

The blood that was collected from the down mare while on the trailer was submitted to the in-house laboratory for a complete blood count (CBC) and plasma biochemical profile in order to establish baseline values. The biochemical profile helps to evaluate renal and hepatic function, muscle enzyme leakage, protein status, lipid and carbohydrate levels, minerals, acid base parameters, and electrolytes. It is important to rule out metabolic disorders (acute renal or liver disease, electrolyte imbalances, HYPP, etc.) that can manifest as neurologic disease. The CBC is useful for determining whether an infectious process is present, and whether the inflammatory process is acute or chronic. It can also be used to aid in the differentiation of a viral versus a bacterial infection. The spinal tap is not a definitive test for neurologic disease, but rather helps to arrive at a diagnosis based on gross appearance, cell count and protein level. All of these tests were used in conjunction with the physical exam findings to piece together a diagnosis.

The results of the chemistry profile were unremarkable. Magnesium was just below normal at 1.5mg/deciliter (dL) (reference range 1.6 - 2.3) which is likely a result of her recent anorexia. Glucose was mildly elevated at 154 mg/dL (reference range 52 - 121) which commonly occurs as a stress response due to the gluconeogenic effects of the naturally occurring stress steroid, cortisol. The total protein was elevated at 9.1 g/dL (reference range 5.2 - 8.2) while the albumin as slightly low at 2.6 g/dL (reference range 2.8 - 3.8). In the dehydrated animal, both TP and albumin would be high. As Missy presented with a normal PCV, we can infer that the elevation in total protein could be due to chronic inflammation. The elevated total bilirubin at 4.1 mg/dL (reference range 0.4 - 3.3) was likely due to anorexia. The precise mechanism is unknown, but possible that there is a decreased uptake of bilirubin or that the conjugation of bilirubin to glucose is impaired due to low glucose levels in the hepatocytes.

The CBC results proved a little more significant, as she did have a leukocytosis 14.92×10^3 cells per microliter (uL) (reference range 5 - 12.5) with a neutrophilia 9.101×10^3 cells/uL (reference range 2.7 – 6.7). Her fibrinogen was also elevated at 500 mg/dL (reference range 100 - 400). These findings are consistent with inflammation.

The CSF tap was the most remarkable of the diagnostic tests obtained. Upon collection, the yellow discoloration (xanthochromia) was evident to the attending large animal hospital (LAH) staff and was explained as a finding supportive of an EHV-1 infection. The laboratory analysis of the CSF confirmed the discoloration and measured the total protein at 161 mg/dL. The cellular components were also measured and resulted in RBC = 2 /uL and Total Nucleated Cell Count (TNCC) = 5/uL. Normal CSF from large animals should contain less than 6 WBC per deciliter, and normal CSF protein concentration in the horse should be below 100 mg/dL.

The elevated protein found in our spinal tap can be explained by the fact that the lesion responsible for the neurologic signs results from a vasculitis which would lead to inflammation and protein 'leakage' through damaged vessels into the CSF (discussed later). Xanthochromia is often present with EHV infections, as it results from denatured heme pigment, although it can also result from contamination of the sample with blood. According to literature available at the Indiana Animal Disease Diagnostic Laboratory, horses positive for EHV often have xanthochromic looking CSF with elevated protein and a normal nucleated cell count. Missy presented with exactly these findings, and no other differentials were listed in the medical record.

In addition to the tests listed above, both blood and a nasal swab were submitted to the Wisconsin Veterinary Diagnostic Laboratory for confirmation of EHV-1 and EHV-4 by real time polymerase chain reaction (PCR). Results were not available until November 12, 2007 but both nasal swab and blood tested negative for the virus. Knowing that it is difficult to isolate the EHV due to its short viremic period, these negative results did not change the differential diagnosis, nor alter the plan for treatment.

The last procedure performed that was of diagnostic significance was the manual evacuation of the bladder and rectum. A large volume of urine was obtained with the stallion catheter, and manure was evacuated manually from the rectum, which was not surprising, as horses with EHV-1 often present with bladder and rectal distention associated with the hind end paresis. These findings supported the initial admitting diagnosis of a herpesvirus infection and will be discussed later.

PLAN

Following the initial assessment upon presentation and results of the CBC, biochemical

profile and the CSF analysis, the VMTH attending veterinarian formulated a plan that was acceptable with the owner. After the necessary consents were authorized, we began Missy on the following therapeutic regime for the remainder of the evening. From the pharmacy, VMTH staff prepared the following medications:

- Potassium penicillin 22,000 international units (IU)/kg IV QID
- Gentamicin 6.6 mg/kg IV once daily
- Dexamethasone 50mg IV once daily
- Thiamine infusion of 450 mg in 1 liter (L) of 5% dextrose given over 30 minutes once daily
- Dimethylsulfoxide (DMSO) 1g/kg in 5 L Normosol at 1 L per hour SID

The evening of admission on November 10, 2008, Missy was still observed to be straining to urinate and was unable to evacuate neither her bladder, nor her rectum. Bruxism was observed, and she relied heavily on the sling for support of her rear limbs.

At approximately 4:00 am on November 11, 2008 (day 2), it was noted by the overnight technical staff that Missy did produce a large amount of hematuria with blood clots present at the end of the urination. At 8:00 that morning, the student reported one normal pile of manure in the stall. The student also commented that the mare was more alert and responsive with no hypersalivation evident. She was standing quietly in the sling and appeared to be relying on it less for support than the day prior.

Treatment was continued the same as on November 10, with the addition of Normosol-R plus 20 milliequivalents (mEq) of potassium chloride (KCl) added per liter. The fluid rate was determined using the adult maintenance rate of 50ml/kg/day, which calculated to 937 ml/hour, or

approximately 1 liter per hour. The fluid type was determined based on the fact that Missy's electrolytes were normal and there was no evidence of an acid-base disturbance. A packed cell volume and total protein (PCV/TP) was also added to her daily orders so that fluid hydration level could be monitored. Physical exam parameters remained within normal limits on day 2 of hospitalization, with the exception of periods of tachypnea when her heart rate reached a high of 60 beats per minute. She was observed eating hay, indicating an improvement in appetite. Her PCV/TP remained constant at 34% and 8.2 mg/dL.

On day 3 of hospitalization (November 12, 2007) Missy's physical exam parameters were again within normal limits, and based on her attitude she appeared to be improving. She was able to stand, but remained mildly ataxic, relying on the sling for some support. The dexamethasone was decreased to 25 mg, once daily and the gentamicin and potassium penicillin were both discontinued due to the owner's limited budget. Her PCV/TP was checked in the morning only and remained the nearly same at 34% and 8.4mg/dL. Her bladder was evacuated manually in the morning, but she did urinate twice on her own later that afternoon and evening. Two normal piles of manure were also observed in her stall in the late afternoon and evening, respectively. Mild urine scalding was noted on the medial aspect of the mare's hind legs. This area was cleaned, and petroleum jelly was applied to protect the skin from further irritation.

On day 4 of her stay at the VMTH (November 13, 2007) Missy received her last doses of thiamine and DMSO. She remained on IV fluid therapy, and received a fourth dose of dexamethasone (25 mg). Her bladder and rectum were not evacuated, as she had been observed urinating and defecating normally on her own. Because of the marked improvement of her neurologic deficits, Missy was taken out of the sling and was observed to walk, turn, lie down

and stand up in her stall without assistance. Her appetite and attitude continued to improve, and her discharge instructions were planned.

On day 5 of hospitalization (November 14, 2007) Missy received her last dose of dexamethasone (25mg) in the hospital and was discontinued from all other treatments. Her discharge instructions were written, with orders to continue oral dexamethasone at 24 mg once every other day for 10 treatments. The discharge instructions indicated the side effects of steroidal therapy (laminitis) and while the exact etiology of the neurologic symptoms was not determined, an infection caused by EHV-1 was listed as the only differential.

CASE DISCUSSION

The equine herpesvirus, also known as Rhinopneumonitis, is widespread within the equine population, and causes many illnesses in horses including abortion, neonatal death, respiratory disease, and neurologic disease. While cases of this disease have been documented, trends indicate that the frequency of the neurologic form seem to be increasing at an alarming pace. Of the 8 types of known herpesviruses, it is the equine herpesvirus 1 (EHV-1) which is responsible for causing the devastating neurologic form of the disease, properly known as Equine Herpes Myeloencephalopathy (EHM). Because EHV-1 is known to have a latent state lasting up to several months or years, clinical manifestations of disease may not immediately follow initial infection. Many horses, it is believed, are infected within the first year of life, but the neurologic form of the disease seems to occur in adulthood resultant from recrudescence and possibly mutation of the virus during periods of stress. This disease is of significant consequence as it occurs as widespread outbreaks, in addition to single isolated occurrences.

EHV-1 is transmitted through the respiratory tract via inhalation of aerosolized

secretions, direct contact, and fomites. The virus attaches to mucosal epithelial cells where replication occurs. After dissemination to the lymphoid tissue, the virus then spreads throughout the body via monocytes and lymphocytes. During the short viremic phase, replication occurs in the vascular endothelial cells. Neurologic disease is due to a vasculitis resulting from immune complex formation, rather than a direct viral infection of the nervous tissue. It is this resultant vasculitis and thrombosis of the arterioles in the spinal cord and brain that lead to the clinical neurologic signs of the disease. Recent research also suggests that there is a specific gene mutation of the EHV-1 that is responsible for the neurologic form of the disease, and tests are being developed for the positive identification of this gene.

Upon initial infection with the EHV-1, the horse may show mild respiratory signs, such as a watery nasal discharge, cough or fever, and then exhibit an acute onset of neurologic signs from 6 to 10 days after initial infection. Neurologic signs can manifest as a wide range of symptoms including vestibular and cranial nerve deficits, blindness and seizures. The signs most commonly associated with EHM include:

- Incoordination and gait abnormalities
- Symmetrical weakness or paresis of the hind end or recumbency
- Inability to rise from the sitting position, classically known as “dog sitting”
- Loss of tail and anal tone resulting in fecal incontinence
- Bladder atony leading to urine scalding

Prognosis for the disease is much better for animals that do not become recumbent. Neurologic signs often progress rapidly for about 48 hours and then stabilize. Many horses show improvement within 5 to 7 days, but full recovery may take months to years, with no guarantee

of return to normal gait or eliminatory function.

Treatment for the horse with EHM is largely supportive therapy, with manual evacuation of bladder and rectum recommended at least twice daily. Location of the lesion can explain the reason for the inability to urinate or defecate normally. Lesions located in the thoracolumbar region (T3 to L3) produce normal front end activity and proprioceptive deficits in the rear resulting in ataxia, abduction, adduction, interference etc. When the lesion in this area is complete, the animal becomes recumbent and periodically assumes a “dog sitting” posture, with exaggerated muscle tone in the hindlimbs. The urinary bladder is distended, but urethral sphincter tone remains normal, hence there is no dribbling of urine. Lesions located in the lumbosacral area (L3 to S2) result in paraparesis or paraplegia. Within the L3 to L6 area, lesions will also cause bladder distention where emptying occurs only when the pressure exceeds that of the sphincter. Urine scalding is present in these cases. Comparing this to the caudal area of the lumbosacral region between S1 and S2, we find that the bladder will actually become flaccid and urine may drip continuously from the vulva. Finally, lesions in the sacrococcygeal area (S3 to Cd5) produce desensitization of the tail and vulva with decreased anal tone. Because the urethral orifice is dilated, urine will constantly leak from the vulva producing urine scalding on the rear end of the animal. In these cases, the horse is unable to evacuate either bladder or rectum.

It is impossible to know the exact location of Missy’s lesion. We can, however, state that she appeared to have a focal lesion, meaning that it affected only one area of the body since both cranial nerves and front limb reflexes appeared normal. Based on the descriptions above, her lesion was likely in the cranial lumbosacral region, as she presented with hind end paresis and bladder distension with increased urethral tone, necessitating manual evacuation. While the

rectum was also evacuated on admission, the mare appeared to be producing manure on her own by the next day. Her bladder continued to be manually evacuated through day 3 of hospitalization.

Besides supportive therapy for the treatment of EHM, textbook recommendations report that the use of anti-inflammatory drugs (corticosteroids) is warranted. Dexamethasone is recommended at 0.05 to 0.1mg/kg IV once or twice daily for 3 to 5 days followed by a tapered dose for an additional 1 to 3 days. Missy received 50 mg of dexamethasone (approximately the 0.1 mg/kg dose) for 2 days and then half the dose (25 mg) for two additional days. Side effects of glucocorticoid administration can vary, as this drug has an effect on nearly every cell type and system in mammals. Laminitis may be induced in horses following high levels of corticosteroid administration due to digital vasoconstriction. It is believed that glucose intolerance and epinephrine, concurrent with administration of the drug, may play a role in the development of this condition.

In clinical situations of neurologic disease, the use of Dimethyl Sulfoxide (DMSO) is routinely prescribed although its efficacy has not been documented. DMSO is used for its anti-inflammatory properties, as well as to reduce the number of cellular damaging free radicals present within the system. Recommended levels are 1 to 2 g/kg IV at a slow rate infusion every 12 to 24 hours. Missy received 450 grams IV (the 1g/kg dose) over 5 hours.

The use of antibiotics was employed because it is generally known that glucocorticoids such as dexamethasone have immunosuppressive effects. Antimicrobial coverage would presumably thwart a secondary bacterial infection of the lungs due to respiratory involvement of the virus, or from the urinary catheterization. Antibiotics are also indicated in recumbent

patients and are used for protection from secondary infections resulting from decubital ulcers and/or sling sores. While Missy was standing and therefore not at risk for decubital ulcer formation, sling placement was monitored carefully to avoid sores. Potassium penicillin and gentamicin were used together to provide broad spectrum coverage of gram positive and gram negative bacteria, respectively.

Thiamine (Vitamin B1) is involved in carbohydrate metabolism, and is found in the nerves and the brain. While the role of thiamine in the neurologic pathway is unknown, some theories suggest that it is involved with nerve impulses as they travel the sodium/potassium gradient. As such, it is used at the VMTH as a neuroprotctant to maintain normal nerve conduction.

Missy presented to the VMTH as a classic example of EHM caused by EHV-1. She was recumbent on the trailer and exhibited bladder atony with increased sphincter tone upon presentation. As a performance horse, she traveled frequently to shows which, combined with the move from Canada to the United States earlier in the year, were likely causes of stress. Her CSF fluid showed the characteristic xanthochromia and high protein indicative of an infection with EHV-1. While neither her nasal swabs nor blood samples showed evidence of the disease, her response to treatment within the given time frame seemed to support a diagnosis of EHM. She was treated in a very straightforward manner, with medications following text book recommendations, and was discharged on November 14, 2007 (four days after initial hospitalization) to a very grateful owner.

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Appendix 1: Plasma biochemical profile

DATE	TEST	RESULT	UNITS	REFERENCE RANGE
11/10/07	Sodium	137.0	mmol/L	130-144
	Potassium	3.3	mmol/L	2.9-5.6
	Chloride	96	mmol/L	92-107
	TCO2	24	mmol/L	21-33
	Anion Gap	20		-
	Calcium	11.7	mg/dL	10.2-13.4
	Phosphorus	4.8	mg/dL	1.7-5.8
	Magnesium	1.5 L	mg/dL	1.6-2.3
	Glucose	154 H	mg/dL	52-121
	Urea Nitrogen	22	mg/dL	9-27
	Creatinine	1.4	mg/dL	0.4-1.9
	Total Protein	9.1 H	g/dL	5.2-8.2
	Albumin	2.6 L	g/dL	2.8-3.8
	Globulin	6.5	g/dL	-
	Alkaline Phosphatase	114	U/L	86-262
	Creatine Kinase	279	U/L	96-620
	AST	163	U/L	156-597
	Gamma GT	10	U/L	5-51
	Cholesterol	109	mg/dL	59-125
	Total Bilirubin	4.1 H	mg/dL	0.4-3.3

Appendix 2: Complete Blood Count

DATE	TEST	RESULT	UNITS	REFERENCE RANGE
11/10/08	Specimen Appearance	Normal		-
	Plasma Appearance	Normal		-
	Total Plasma Protein	9.1 H	g/dL	6-8.5
	Fibrinogen	500 H	mg/dL	100-400
	RBC	8.36	X 10 ⁶ / uL	6.8-12.9
	Hemoglobin	14.2	g/dL	11-19
	RBC Hemoglobin	13.6	g/dL	11-19

Appendix 3: Cytology - Cerebrospinal Fluid

DATE	TEST	RESULT	UNITS	REFERENCE RANGE
11/10/07	Color	Xanthochromic		-
	Appearance	Clear		-
	Total Protein	161.0	mg/dL	-
	RBC	2	Cells/uL	-
	TNCC	5	Cells/uL	-
	Neutropils	2	%	-
	Lymphocytes	79	%	-
	Mononuclear Cells	19	%	-
	Cytology Microscopic: Nucleated cell count is within reference interval. The majority of cells are small lymphocytes and mononuclear cells (mostly monocytoid cells). A small number of neutrophils and erythrocytes are present. The protein concentration is slightly to moderately increased. Organisms are not seen.			
	Interpretation: Xanthochromia usually indicates prior hemorrhage in the intrathecal space, which could also explain the increased protein concentration. Erythrophagia is not observed.			

Appendix 4 : Immunology and Virology Herpes I and IV by PCR

DATE	SOURCE	TEST	RESULT	COMMENTS
11/12/07	Respiratory tract upper	EHV-1 by PCR	Negative	
		EHV-4 by PCR	Negative	

Appendix 5 : Immunology and Virology – Virus Isolation Equine

DATE	SOURCE	TEST	RESULT	COMMENTS
11/12/07	Pharyngeal Swab	EHV-1 by PCR	Negative	
	Blood	EHV-1 by PCR	Negative	
<p>Real time PCR assays double the amount of nucleic acid in a cycle which consists of high temperature amplification of DNA. Usually 40 cycles are performed. The CT (cycle threshold) is defined as the number of cycles required for the fluorescent signal to exceed background level.</p> <p>CT value = 0 –negative sample—no target nucleic acid detected</p>				