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Approach the Horse with a Suspected Myopathy

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The diagnosis of muscle diseases in horses is based on a thorough history, careful physical examination, a complete blood count and a serum biochemistry profile. Following this evaluation, it can often be determined if muscular signs are part of a primary or secondary disease process. Primary muscle disorders usually fall into one of five broad clinical categories: 1) focal muscle strain 2) rhabdomyolysis, 3) weakness and exercise intolerance without rhabdomyolysis, 4) abnormal muscle contraction/conduction 5) muscle atrophy. Further diagnostic tests can then be selected to localize the muscle groups affected by the disorder and to identify the disease process that is causing the presenting clinical signs.

History and Physical Examination

A detailed history is often required when assessing muscle disorders in horses because many disorders are intermittent in nature and triggered by certain environmental stimuli. Important aspects include:

- muscle tone, muscle mass
- muscle pain/soreness
- gait abnormalities
- exercise intolerance
- weakness
- duration and frequency of signs

Further characterization of possible eliciting factors requires a detailed account of the horse's exercise schedule, diet, vaccination history, signs of concurrent disease, and current medications.

Inspection of the horse at a distance for symmetry of muscle mass while the horse is standing with forelimbs and hind limbs exactly square is imperative to assess muscle mass, symmetry and signs of atrophy. Subsequently, palpation of the entire muscle mass of the horse provides valuable information regarding muscle tone, heat, pain, swelling, subtle muscle atrophy, and fasciculations. The triceps, pectoral, gluteal and semitendinosus muscles can be tapped with a fist or percussion hammer and observed for a prolonged contracture suggestive of myotonia. Running a blunt instrument such as a hemostat, a needle cap, or a pen over the lumbar and gluteal muscles provides information regarding back pain. Extension (swayback) followed by flexion (hogback) of the back is expected in healthy animals. A lameness evaluation, including flexion tests, is often indicated as part of evaluation of the muscular system as muscle pain may be secondary to lower limb lameness. The horse should be observed at a walk or trot for any gait abnormalities and in some

cases lounged for 15 minutes or ridden until clinical signs are elicited. Any signs of neurologic disease should also be followed up by a detailed neurologic examination.

Biochemical profiles

Skeletal muscle necrosis may be identified by determining the activity in serum of creatine kinase (CK) and aspartate transaminase (AST).

Serum CK: Limited elevations in CK (< 1000 U/L) may accompany training or transport. Extreme fatiguing exercise (e.g., endurance rides or the cross-country phase of a three-day event) may result in CK activities being increased to more than 1000 U/L, but usually less than 5000 U/L. Under these circumstances, serum CK activities rapidly return to baseline (i.e., less than 350 IU/L in 24 to 48 hours). Recumbent animals also may have slightly elevated CK activities that are usually <3000 U/L. In contrast, more substantial elevations (from several thousand to hundreds of thousands of U/L) in the activity of this enzyme may occur with rhabdomyolysis.

Serum AST: Serum AST, previously known as (SGOT), has high activity in skeletal and cardiac muscle and also in liver, red blood cells, and other tissues. Elevations in AST are not specific for myonecrosis, and increases could be the result of hemolysis, muscle, liver, or other organ damage. AST activity peaks between 12 to 24 hours after the insult.⁴ In addition, AST may persist for two to three weeks after rhabdomyolysis.

Comparing serial activities of CK and AST provides information concerning the progression of myonecrosis. Combined elevations in CK and AST reflect relatively recent or active myonecrosis; persistently elevated serum CK indicates that myonecrosis is likely to be continuing. Elevated AST activity accompanied by decreasing or normal CK activity indicates that myonecrosis has ceased. The degree of elevation of CK and AST does not necessarily reflect the severity of clinical signs.

Vitamin E and selenium concentrations: Whole blood selenium concentrations or glutathione peroxidase measured in EDTA or heparin tubes are of value in assessing muscle disorder in animals housed in areas deficient in selenium. Vitamin E concentration can be measured in serum samples; however, variability in serum levels can be quite large and pooling of several samples is often recommended to accurately assess a deficiency.

Urinalysis

Urine can be obtained free catch from horses placed in stalls with fresh bedding or via catheterization of mares without tranquilization. Urinalysis is particularly important in horses with myoglobinuria, elevations in creatinine, or suspected electrolyte imbalances. Urine specific gravity, protein content, WBC count, RBC count, and evaluation of cast formation should be performed to assess the potential for concurrent renal disease. A positive hemastix test (orthotoluidine) in the absence hemolysis or RBCs in urine is highly suggestive of myoglobinuria.

Renal fractional excretion of electrolytes: Determination of electrolyte, mineral, and creatinine concentrations in urine and blood may be useful to

determine electrolyte balance in horses with muscle cramping or exertional rhabdomyolysis.¹¹⁻¹³ Values below the reported ranges are suggestive of conservation and possibly inadequate dietary intake that may require supplementation although wide variations can occur between and within individual horses.¹¹⁻¹⁴

Renal fractional excretions (FE) can be calculated using the following formula. Where X= measured electrolyte and Cr creatinine.

$$FE\% (X) = \left(\frac{[Cr]_{\text{plasma}}}{[Cr]_{\text{urine}}} \times \frac{[X]_{\text{urine}}}{[X]_{\text{plasma}}} \right) \times 100$$

Normal values for FE of electrolytes are dependant on a horse's diet. Normal values in acidified urine (%) for horses consuming grass hay and a sweet feed mix with available salt are: FE_{Na} 0.04-0.08, FE_K 35-80, FE_{Cl} 0.4-1.2, FE_{Ca} 5.3-14.5, FE_P 0.05-4.1, FE_{Mg} 14.2-21.4¹¹

Exercise response test

Diagnosing chronic exertional rhabdomyolysis may be problematic in horses that do not have acute clinical signs and have normal serum AST and CK at rest. In such cases, an exercise challenge can be helpful in detecting subclinical exertional rhabdomyolysis. In addition, quantifying the extent of rhabdomyolysis during mild exercise is helpful in deciding how rapidly to put a horse back into training. Blood samples should be taken before exercise and about four to six hours after exercise to evaluate peak changes in CK.^{4, 5} Serum CK activity measured immediately post-exercise will not reflect the amount of damage occurring during the exercise test.⁴ Fifteen minutes of trotting is often sufficient to produce subclinical muscle damage in horses prone to exertional myopathies.¹⁷ If signs of stiffness develop before this, exercise should be concluded. A normal response would be less than a three- to four-fold increase from basal CK.

Ultrasonography

Diagnostic ultrasonography is potentially very useful for identification of muscle trauma and fibrosis, provided there is physical disruption of the muscle. Careful comparisons must be made between similar sites in contralateral limbs, in both transverse and longitudinal images because the typical striated echogenic pattern varies according to the muscle group.²² The appearance of muscle is also sensitive to the way the horse is standing and whether the muscle is under tension, so it is important that the horse is standing squarely and bearing weight evenly.

In an acute injury, muscle fiber disruption is seen as relatively hypoechoic areas within muscle, with loss of the normal muscle striation. The jagged edge of the margin of the torn muscle may be increased in echogenicity. Tears in the muscle fascia may be identified. The defect in muscle may be filled by a loculated haematoma that is slowly

replaced by hypoechoic granulation tissue. Muscle repair shows a progressive increase in echogenicity. Relatively hyperechoic regions may develop due to fibrous scarring. Hyperechoic regions causing shadowing artefacts reflect mineralization.

Electromyography (EMG)

A specific diagnosis of the cause of muscle atrophy, muscle fasciculations, or myotonic dimpling after tapping the muscle can be aided by performing EMG.^{23, 24} EMG of normal skeletal muscle shows a brief burst of electrical activity when the needle is inserted in muscle and then quiescence, unless motor units are recruited (motor unit action potentials), or the needle is very close to a motor end plate (miniature end plate potentials). Normal muscle shows little spontaneous electrical activity unless the muscle contracts or the horse moves. Horses with abnormalities in the electrical conduction system of muscle, or denervation of motor units, show abnormal spontaneous electrical activity in the form of fibrillation potentials, positive sharp waves, myotonic discharges, or complex repetitive discharges. Specific patterns of waveforms may indicate specific disorders such as denervation atrophy, HYPP or myotonia.²⁵⁻²⁹

Muscle biopsy

There have been many recent advances in obtaining diagnostic information regarding specific muscle disease by using the muscle biopsy technique.³⁰⁻³⁴ Specialized laboratories are often most helpful in processing frozen muscle biopsies and interpreting muscle pathology in order to provide a specific diagnosis and treatment. See <http://www.cvm.umn.edu/umec/lab/home.html>.

The selection of an appropriate muscle to biopsy is of importance in obtaining the best diagnostic information.¹ With exertional rhabdomyolysis, samples of the semimembranosus muscle and gluteus medius muscle often examined because of their consistent involvement in exertional rhabdomyolysis and ease of collection with open and needle biopsy techniques, respectively.^{32, 34} An open surgical biopsy of the semimembranosus muscle is usually obtained in veterinary practice because of the ease of orienting a longitudinal biopsy and ease of treating complications such as dehiscence. A site approximately eight cm distal to the tuber ischii provides ample muscle tissue without leaving a readily evident scar should dehiscence occur. The biopsy is performed using sedation and local anesthesia directed into the subcutaneous, but not muscle, tissue. Following a vertical incision in the skin and muscle fascia, two parallel incisions two cm apart and four to five cm long are made in the muscle. The muscle is grasped in one dorsal corner using forceps to avoid crushing other portions of the biopsy. A cross-sectioning incision is made dorsally, the muscle sample is excised in a ventral direction to a depth of one to two cm and the sample is excised ventrally. Preparation of the sample for shipment is described below. Good closure of fascia and subcutaneous tissue is the key to prevent

¹ <http://www.cvm.umn.edu/umec/lab/home.html>

dehiscence. Staples or non-absorbable skin sutures are used to close the skin. Horses need to be stall rested for two to four days following this biopsy procedure and sutures removed in 10-14 days.

A few muscle disorders are amenable to evaluation using Trucut biopsy samples. This is best applied to diffuse disorders, such as immune-mediated myopathies, that affect muscles such as epaxial or gluteal muscles that are difficult to sample using open surgical techniques. Several Trucut biopsies placed in formalin are required. Trucut samples are not of value in assessing samples from horses with exertional rhabdomyolysis or equine motor neuron disease, as they do not provide an adequate sample size to make a diagnosis.

Sample preparation: Prior to obtaining a muscle biopsy, the laboratory where samples will be evaluated should be contacted to determine their preferred method of fixation. Many laboratories specializing in neuromuscular diseases prefer to obtain samples that are fresh within 24 hours of sampling, as frozen sections provide better preservation and visualization of muscle properties. Upon arrival in the laboratory, these fresh samples are prepared for freezing in isopentane suspended in liquid nitrogen. Preparation of samples for shipment includes wrapping the muscle in gauze moistened with saline (damp, not soaking wet) and placement in a small plastic container. Samples are shipped overnight express on icepacks in a Styrofoam container. Laboratories that use formalin fixation avoid the requirement for more intensive preparation required for frozen samples; however, formalin fixation has the disadvantage of creating a number of artifacts including cracking, sedimentation, and leaching of glycogen that make it less than ideal.

Genetic testing

A DNA test² is available to identify horses with the dominant mutation for HYPP found in the extended pedigree of "Impressive" descendants. Mane or tail hairs with intact roots are submitted for analysis to determine if horses are normal, heterozygous, or homozygous for HYPP. Other genetic mutations in other bloodlines that might cause HYPP are not detected by this test.

A DNA test³ is also available to identify foals or aborted feti that are homozygous for the fatal neonatal disorder glycogen branching enzyme deficiency (GBED) and horses that are carriers. Rapid diagnosis is often made most readily by identifying abnormal polysaccharide globules in PAS stains of frozen sections.

A definitive diagnosis of type 1 PSSM can be made by genetic testing for the *GYS1* mutation. Genetic testing is performed on hair roots or whole blood samples at the Veterinary Diagnostic Laboratory at the University of Minnesota. (www.vdl.umn.edu/vdl/ourservices/neuromuscular.html). If horses test negative for the *GYS1* mutation, a muscle biopsy will be required to identify abnormal polysaccharide accumulation characteristic for type 2 PSSM.

Based on the information obtained by this type of thorough evaluation, a

^c www.vgl.ucdavis.edu

diagnosis can usually be obtained. The following classification system may be helpful in narrowing down rule-outs for muscle disease in horses.

Classification of muscle disorders

TABLE 1.22720

Non-exercise-associated Rhabdomyolysis

- Inflammatory myopathies
- Clostridial myositis
- Influenza myositis
 - Sarcocystis* myositis
- Immune-mediated myopathy
- Nutritional myopathy
 - Vitamin E and selenium deficiency
- Toxic myopathy
 - Ionophore toxicity
 - Pasture myopathies
 - Rayless goldenrod/white snakeroot
 - Cassia occidentalis*
 - Atypical myoglobinuria
- Traumatic myopathy
 - Compressive anesthetic myopathy
 - Trauma
- Genetic myopathies
 - Glycogen branching enzyme deficiency in Quarter Horses
 - Polysaccharide storage myopathy types 1 and 2
 - Malignant Hyperthermia in Quarter Horses

Exertional Rhabdomyolysis

- Focal muscle strain
- Sporadic tying-up (overexertion)
- Chronic tying-up
 - Dietary imbalances, vitamins, minerals, electrolytes
 - Polysaccharide storage myopathy type 1 and 2
 - Malignant Hyperthermia
 - Recurrent exertional rhabdomyolysis
 - Idiopathic chronic exertional rhabdomyolysis

Exertional Myopathy with Normal CK

- Mitochondrial myopathy

Muscle Atrophy

- Myogenic atrophy
 - Severe rhabdomyolysis
 - Disuse
 - Cushing's disease
 - Immune-mediated myositis (rapid atrophy)
 - Polysaccharide storage myopathy
- Neurogenic atrophy
 - Equine protozoal myelitis
 - Local nerve trauma
 - Equine motor neuron disease

Muscle Fasciculations

Pain, Fear

Weakness (botulism, chronic debilitation)

Electrolyte abnormalities

Equine motor neuron disease

Hyperkalemic periodic paralysis

Hypokalemia

Otobius megnini (ear tick) infestation

Myotonic dystrophy

Stiff horse syndrome

Shivers

Conflict of interest statement

Drs. Valberg, Mickelson and McCue own the license for PSSM testing and receive sales income from its use. Their financial and business interests have been reviewed and managed by the University in accordance with its conflict of interest policies.

References

1. Cardinet GH, Littrell JF, Freedland RA. Comparative investigations of serum creatine phosphokinase and glutamic-oxaloacetic transaminase activities in equine paralytic myoglobinuria. *Res Vet Sci.* 1967;8:219-226.
2. Nishita T, Ohohashi T, Asari M. Determination of carbonic anhydrase III isoenzyme concentration in sera of racehorses with exertional rhabdomyolysis. *Am J Vet Res.* 1995;56:162-166.
3. Holmgren N, Valberg S. Measurement of serum myoglobin concentrations in horses by immunodiffusion. *Am J Vet Res.* 1992;53:957-960.
4. Valberg S, Jonsson L, Lindholm A, Holmgren N. Muscle histopathology and plasma aspartate aminotransferase, creatine kinase and myoglobin changes with exercise in horses with recurrent exertional rhabdomyolysis. *Equine Vet J.* 1993;25:11-16.
5. Volfinger L, Lassourd V, Michaux JM, Braun JP, Toutain PL. Kinetic evaluation of muscle damage during exercise by calculation of amount of creatine kinase released. *Am J Physiol.* 1994;266:R434-41.
6. Anderson MG. The effect of exercise on the lactic dehydrogenase and creatine kinase isoenzyme composition of horse serum. *Res Vet Sci.* 1976;20:191-196.
7. Argiroudis SA, Kent JE, Blackmore DJ. Observations on the isoenzymes of creatine kinase in equine serum and tissues. *Equine Vet J.* 1982;14:317-321.
8. Hatzipanagiotou A, Lindner A, Sommer H. LDH and CK isoenzyme patterns in the blood plasma of horses with elevated CK, LDH and AST activities. *Dtsch Tierarztl Wochenschr.* 1991;98:284-286.
9. Rowland LP, Penn AS. Myoglobinuria. *Med Clin North Am.* 1972;56:1233-1256.
10. Rasanen LA. Exercise-induced purine nucleotide degradation and changes in myocellular protein release. *Equine Vet Suppl.* 1995;18:235-238.
11. McKenzie EC, Valberg SJ, Godden SM, et al. Comparison of volumetric urine collection versus single-sample urine collection in horses consuming diets varying in cation-anion balance. *Am J Vet Res.* 2003;64:284-291.
12. Harris P, Colles C. The use of creatinine clearance ratios in the prevention of equine rhabdomyolysis: A report of four cases. *Equine Vet J.* 1988;20:459-463.
13. Beech J, Lindborg S, Braund KG. Potassium concentrations in muscle, plasma and erythrocytes and urinary fractional excretion in normal horses and those with chronic intermittent exercise-associated rhabdomyolysis. *Res Vet Sci.* 1993;55:43-51.

14. McKenzie EC, Valberg SJ, Godden SM, et al. Plasma and urine electrolyte and mineral concentrations in thoroughbred horses with recurrent exertional rhabdomyolysis after consumption of diets varying in cation-anion balance. *Am J Vet Res.* 2002;63:1053-1060.
15. Harris PA, Snow DH, Greet TR, Rosedale PD. Some factors influencing plasma AST/CK activities in thoroughbred racehorses. *Equine Vet J Suppl.* 1990;(9):66-71.
16. Frauenfelder HC, Rosedale PD, Ricketts SW, Allen WR. Changes in serum muscle enzyme levels associated with training schedules and stage of the oestrous cycle in thoroughbred racehorses. *Equine Vet J.* 1986;18:371-374.
17. Valberg SJ, Mickelson JR, Gallant EM, MacLeay JM, Lentz L, de la Corte F. Exertional rhabdomyolysis in quarter horses and thoroughbreds: One syndrome, multiple aetiologies. *Equine Vet J Suppl.* 1999;30:533-538.
18. Turner TA. Hindlimb muscle strain as a cause of lameness in horses. *Proc Am Assoc equine Pract.* 1989;35:281.
19. Morris E, Seeherman HJ, O'Callaghan MW, Schelling SH, Paradis MR, Steckel RS. Scintigraphic identification of skeletal muscle damage in horses 24 hours after strenuous exercise. *Equine Vet J.* 1991;23:347-352.
20. Matin P. Basic principles of nuclear medicine techniques for detection and evaluation of trauma and sports medicine injuries. *Semin Nucl Med.* 1988;18:90-112.
21. Valberg SJ, Dyson SJ. Skeletal muscle and lameness. In: Ross MW, Dyson SJ, eds. *Diagnosis and Management of Lameness in the Horse.* 1st ed. St.Louis MO: Saunders; 2003:723-743.
22. Reef V. Musculoskeletal ultrasonography. In: *Equine Diagnostic Ultrasound.* Philadelphia PA: WB Saunders; 1998.
23. Wijnberg ID, Back W, de Jong M, Zuidhof MC, van den Belt AJ, van der Kolk JH. The role of electromyography in clinical diagnosis of neuromuscular locomotor problems in the horse. *Equine Vet J.* 2004;36:718-722.
24. Wijnberg ID, Franssen H, Jansen GH, Back W, van der Kolk JH. Quantitative electromyographic examination in myogenic disorders of 6 horses. *J Vet Intern Med.* 2003;17:185-193.
25. Montagna P, Liguori R, Monari L, et al. Equine muscular dystrophy with myotonia. *Clin Neurophysiol.* 2001;112:294-299.
26. Naylor JM, Robinson JA, Crichlow EC, Steiss JE. Inheritance of myotonic discharges in american quarter horses and the relationship to hyperkalemic periodic paralysis. *Can J*

Vet Res. 1992;56:62-66.

27. Robinson JA, Naylor JM, Crichlow EC. Use of electromyography for the diagnosis of equine hyperkalemic periodic paresis. *Can J Vet Res.* 1990;54:495-500.

28. Reed SM, Hegreberg GA, Bayly WM, Brown CM, Paradis MR, Clemmons RM. Progressive myotonia in foals resembling human dystrophia myotonica. *Muscle Nerve.* 1988;11:291-296.

29. Steinberg S, Botelho S. Myotonia in a horse. *Science.* 1962;137:979-980.

30. Firshman AM, Valberg SJ, Bender JB, Annandale EJ, Hayden DW. Comparison of histopathologic criteria and skeletal muscle fixation techniques for the diagnosis of polysaccharide storage myopathy in horses. *Vet Pathol.* 2006;(in press).

31. Valberg SJ, MacLeay JM, Mickelson JR. Polysaccharide storage myopathy associated with exertional rhabdomyolysis in horses. *Comp Cont Educ.* 1997;19:1077-1086.

32. McCue M, Ribiero W, Lewis S, Valberg SJ. Prevalence of polysaccharide storage myopathy in horses with neuromuscular disorders. *Equine Vet J suppl.* (in press).

33. Valentine BA, McDonough SP, Chang YF, Vonderchek AJ. Polysaccharide storage myopathy in morgan, arabian, and standardbred related horses and welsh-cross ponies. *Vet Pathol.* 2000;37:193-196.

34. Ledwith A, McGowan CM. Muscle biopsy: A routine diagnostic procedure. *Equine Vet Educ.* 2004;April:84-89.

Figure 1





Figure 2



Figure 3