

Large Animal VETERINARY Rounds®

SEPTEMBER 2008
Volume 8, Issue 7

AS PRESENTED IN THE ROUNDS OF THE DEPARTMENT OF LARGE ANIMAL CLINICAL SCIENCES
OF THE WESTERN COLLEGE OF VETERINARY MEDICINE, UNIVERSITY OF SASKATCHEWAN

Equine Myopathies: An Update (Part 1)

By Katharina Lohmann, DVM, PhD, Diplomate ACVIM

Rhabdomyolysis, also known as the “tying-up” syndrome, has been known to horse owners and veterinarians for many years; however, recent research has elucidated several underlying myopathies and provided evidence for their genetic basis. “New” diseases such as glycogen-branching enzyme deficiency have also been described and their genetic basis identified. This issue of *Large Animal Veterinary Rounds* provides an overview of myopathies in horses, with a focus on exertional rhabdomyolyses. A subsequent issue will discuss nonexertional rhabdomyolyses and will include a review of other myopathies not associated with rhabdomyolysis.

Myopathies, or disorders affecting the musculature, play a significant role in equine medicine because they are commonly associated with a decrease in performance and, therefore, the use of the affected horse. Valberg¹ divides myopathies into those causing rhabdomyolysis, muscle atrophy, abnormal muscle twitching, and muscle weakness or exercise intolerance.

The rhabdomyolysis complex (Greek – *rhabdo* = striped/striated; *myo* = muscle; *lysis* = breakdown) comprises disorders that result in muscle-cell destruction; these are generally characterized by painful muscle cramping and hardening, severe increases in muscle enzymes detectable in serum chemistry tests, and myoglobinuria. Disorders of rhabdomyolysis can be classified according to their relationship to exercise as exertional and nonexertional and, further, according to their specific etiology. A classification system as proposed by Valberg¹ and Aleman² is presented in Table 1.

Sporadic exertional rhabdomyolysis

Exertional rhabdomyolysis, or “tying-up,” typically occurs in horses performing exercise beyond their conditioning status and in horses performing strenuous exercise after a period of rest and inactivity (“Monday morning disease”). Clinical signs are acute; they include a reluctance to move and/or a stiff gait, firm and painful muscles, weakness and fatigue, as well as anxiety indicated by sweating, tachycardia, and tachypnea. Severely affected horses may become recumbent. Myoglobinuria is evident as dark, “coffee coloured” urine; however, the absence of grossly visible urine discoloration does not rule out myoglobinuria. While the pathophysiology of exertional rhabdomyolysis is not well-described in the horse, rhabdomyolysis in humans is attributed to direct injury of the cell membrane during traumatic events (“crush injuries”), muscle-cell hypoxia and adenosine triphosphate (ATP) depletion under anaerobic conditions, and electrolyte disturbances (eg, hypokalemia and hyponatremia) leading to disruption of the cellular sodium-potassium (Na-K) pump function.³ Although rhabdomyolysis in horses has historically been attributed to lactic-acid build-up in the musculature, this mechanism has since been discounted as a primary causative factor because clinical signs generally occur before the onset of anaerobic metabolism during exercise.⁴ Aside from inadequate conditioning and poor management, risk factors for exertional rhabdomyolysis in horses include high carbohydrate intake and concurrent diseases. Vitamin E and/or selenium deficiency, hypothyroidism, and bacterial or viral causes have also been suggested as predisposing causes; however, the evidence concerning the involvement of these factors remains unclear. Female horses appear to be predisposed; this may indicate a role for hormonal factors in the development of rhabdomyolysis.



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The Canadian Veterinary
Medical Association recognizes
the educational value of this
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Table 1: Classification of equine rhabdomyolysis**Exertional rhabdomyolysis**

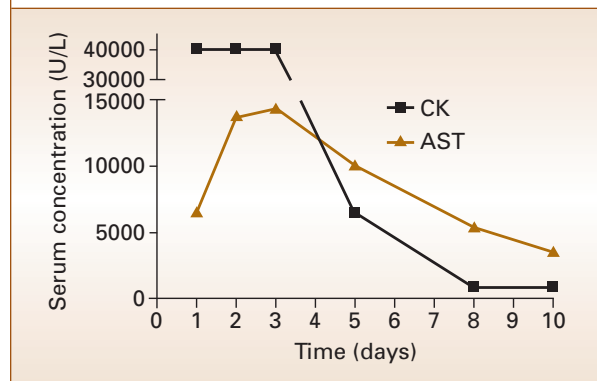
- Sporadic
- Chronic recurrent
 - Polysaccharide storage myopathy
 - Recurrent exertional rhabdomyolysis
 - Idiopathic

Non-exertional rhabdomyolysis

- Nutritional
- Metabolic
 - Glycogen-branching enzyme deficiency
- Associated with inflammation or infection
 - Virus-associated
 - Bacteria-associated
 - Immune-mediated
- Toxic
- Associated with general anesthesia

Differential diagnoses for horses with exertional rhabdomyolysis include lameness, especially laminitis, colic, pleuropneumonia, back pain, and – especially for recumbent animals – neurological diseases. Intravascular hemolysis and bilirubinuria should be considered differentially to myoglobinuria, and laboratory testing should be performed to clarify the cause of urine discoloration. Diagnostic testing should include serum biochemistry for evaluation of muscle enzymes, serum electrolyte concentrations, and renal function parameters, as well as urinalysis. Horses with rhabdomyolysis typically show severe elevations in the muscle enzymes, creatine kinase (CK) and aspartate aminotransferase (AST). Creatine kinase peaks rapidly, approximately 4–6 hours after an insult, and – contrary to other species – has a short half-life of approximately 2 hours. Conversely, AST rises more slowly and peaks 12–24 hours after the insult, and has a long half-life of 7–10 days. The course of enzyme increase and decrease following an episode of severe acute rhabdomyolysis in a Thoroughbred horse is demonstrated in Figure 1. For most laboratories, 40,000 units/L is the maximum limit of detection for CK, and sample dilution may be required to obtain an accurate value. Other sources of the enzymes, such as myocardium for CK and liver tissue for AST, must be taken into account when evaluating biochemistry results. Repeat serum biochemistry testing is valuable for monitoring improvement and response to therapy.

In one study,⁴ the most consistent electrolyte abnormality in horses with exertional rhabdomyolysis was hypochloremia; most horses also revealed mild metabolic alkalosis. The hallmark abnormality on urinalysis of horses with rhabdomyolysis is myoglobinuria; however, without special tests, hemoglobin cannot be distinguished from myoglobin. In the absence of specific testing for myoglobin, laboratories typically diagnose myoglobinuria based on a positive “blood”

Figure 1: Time course of serum creatine kinase (CK) and serum aspartate aminotransferase (AST) in a horse with exertional rhabdomyolysis

Onset of clinical signs and presentation for veterinary examination was on Day 1. Note that the maximum limit of detection for CK was 40,000 units/L; sample dilution would have been necessary to obtain accurate values on days 1–3.

test on the dipstick, absence of erythrocytes in urine sediment, and absence of hemolysis.

Treatment of horses with rhabdomyolysis includes rest, intravenous and/or oral fluid therapy, pain control and, if necessary, sedatives to relieve anxiety. Horses should not be forced to move in the acute stages of severe disease, and a return to exercise should be based on improvement of muscle-enzyme concentrations and the attitude and willingness of the horse to move. Recumbent horses should be placed on soft bedding to prevent injury; they should be encouraged to stand and change sides every few hours or turned, if they are unable to stand. Slings may be considered in select cases. The rationale for fluid therapy is to maintain hydration and treat dehydration if present, correct electrolyte abnormalities, maintain and improve muscle perfusion, and prevent pigment nephropathy. As myoglobin is more soluble in alkaline urine, treatment of metabolic acidosis and maintenance of a urine pH >7.5 is further recommended.⁵ The author generally recommends intravenous fluid therapy for all horses with rhabdomyolysis; the therapy should be continued at 1.5 to 2 times the maintenance rate until the urine is grossly clear, CK values have decreased considerably, and AST values no longer rise.

Nonsteroidal anti-inflammatory drugs such as flunixin meglumine are generally recommended for pain control; however, hydration status and renal function should be taken into consideration before starting therapy. In very dehydrated horses, alternate medications (eg, butorphanol) may be indicated until hydration is improved and urine production increases. Acepromazine has been advocated for the relief of anxiety in affected horses; however, hypotension may ensue with repeated dosing in the absence of appropriate fluid therapy. Other suggested treatments include methocarbamol as a muscle relaxant, dimethyl sulfoxide (DMSO) as an anti-inflammatory and free-radical scavenger, as well as vitamin E and selenium supplementation, if deficiencies are identified.

Prognosis for horses with sporadic exertional rhabdomyolysis is generally favourable, provided that appropriate therapy is instituted in a timely fashion and horses do not develop complications such as renal failure. Recovery time depends on the severity of the initial insult,⁶ and an adequate rest period followed by a gradual return to exercise is recommended following an episode. The author generally suggests to avoid feeding concentrate until horses are back to their previous level of exercise. Owners are also counselled on the importance of proper conditioning and the benefits of regular exercise, preferably including pasture turn-out.

Chronic recurrent rhabdomyolysis

Chronic recurrent rhabdomyolysis represents a group of diseases characterized by recurrent episodes of rhabdomyolysis attributable to underlying myopathies. While this group of disorders is listed under the exertional rhabdomyolyses in Table 1, the severity of the episodes, as well as the intervals between episodes can vary widely, and affected horses typically experience episodes during or after less than strenuous exercise. Some conditions, such as polysaccharide storage myopathy (PSSM), can also cause clinical episodes in the absence of exercise and, therefore, are considered to be metabolic causes of (nonexertional) rhabdomyolysis by some authors.² Among the underlying myopathies identified to date, in some a genetic basis has been established, and it is suspected and under investigation for others. Chronic recurrent rhabdomyolysis requires careful lifelong management of affected horses, and changes in the diet and exercise regimen of these horses are generally required to maintain athletic capability. Despite management, affected horses may be unable to reach high levels of performance (eg, racing), but may fare well in less challenging “occupations.”

Polysaccharide storage myopathy (PSSM)

PSSM is probably the best understood of the equine myopathies; it is a common cause of chronic recurrent rhabdomyolysis in Quarter Horses, Paints, and Appaloosas. It has further been identified in Warmbloods and draft horses, where muscle weakness and atrophy may be the predominant clinical signs,⁷ but rarely in other breeds. PSSM is characterized by increased muscle glycogen content and an accumulation of abnormal polysaccharide in muscles of affected horses; in addition, heightened insulin sensitivity, enhanced glucose clearance from the bloodstream, and increased cellular glucose uptake have been demonstrated.⁸ The structure of abnormal polysaccharide is characterized by long unbranched carbohydrate chains with amylase resistance; abnormal glycogen can be demonstrated using periodic acid-Schiff reaction (PAS) staining of muscle biopsy specimens. Contrary to glycogen-storage diseases in humans, normal glycogen, as well as abnormal polysaccharide can be broken down enzymatically in affected horses, although aerobic glycogen metabolism may be affected.

An autosomal dominant genetic defect underlying PSSM has been identified, representing a 10-base pair substitution in the glycogen synthase 1 gene.⁹ The mutation was identified

in a number of breeds and was particularly common in PSSM-affected Quarter Horses and draft horse-related breeds.¹⁰ An evaluation of muscle biopsy specimens from suspect horses revealed prevalence estimates for the disorder at 6% in Quarter Horses and 36% in Belgian draft horses.^{11,12} An overall prevalence estimate of 6%–12% among overtly healthy Quarter Horses in the United States was also reported.¹³ Although a relationship between PSSM and “shivers” in draft horses has previously been suggested, this could not be proven in the above mentioned study of Belgian draft horses.¹¹

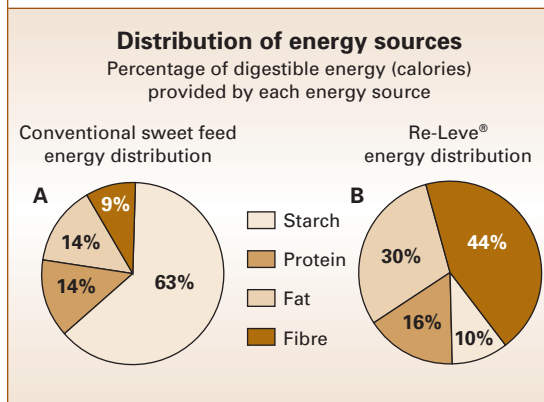
Diagnosis of PSSM is by clinical signs and history, the confirmation of rhabdomyolysis during episodes of muscle cramping, exercise testing, muscle biopsy, and genetic testing. Genetic testing (available at the University of Minnesota¹) is recommended for suspect horses of Quarter Horse, draft horse, Warmblood, and related breeds. Since the mutation occurs with variable frequency in different breeds and is not identified in all clinically affected horses, evaluation of muscle biopsies is also recommended for light horse breeds and for suspect horses testing negative for the mutation. Further information regarding genetic testing is available from the University of Minnesota website.¹

Other causes of recurrent rhabdomyolysis, such as lameness, should be ruled out by careful examination and appropriate diagnostic testing. Serum biochemical testing during an episode will reveal changes similar to exertional rhabdomyolysis (ie, increase in CK and AST noted above), while horses generally have normal or only mildly increased muscle enzymes between episodes. Exercise testing can be performed in suspect horses to reveal a greater than expected increase in muscle enzymes following submaximal exercise. A doubling of CK or more is suggestive of PSSM; however, test accuracy is limited by interindividual variation and the difficulty in establishing submaximal exercise levels for individual horses. The author sometimes recommends exercise testing to increase the suspicion of PSSM before proceeding with a muscle biopsy; exercise testing is also easily performed on a farm, and it may help the owner and veterinarian involved in the decision to refer a horse for further diagnostic testing.

Muscle biopsy is relatively easy to perform technically; it rarely results in major complications and leaves minimal scarring. Biopsy samples are taken from the semimembranosus muscle using an excision technique (a piece, approximately 1 × 1 cm in size, must be obtained); detailed instructions can be obtained from the University of Minnesota website.¹ The most important requirement is that muscle biopsies be submitted to a pathologist experienced in evaluating PSSM; veterinarians must contact the laboratory prior to taking a sample to receive instructions on proper shipping and handling. Since accumulation of abnormal polysaccharide is a sequela rather than a cause of disease and does not occur until later in life, muscle biopsy is not recommended in horses <1 year of age.

While treatment of acute episodes of rhabdomyolysis does not differ significantly in horses with PSSM – one exception is the recommendation to provide mild exercise

Figure 2: Comparison between nutrient distribution in a conventional sweet feed (A) and the Re-Leve® product (B)



Adapted from <http://www.re-leve.com/images/DistributionOfEnergySources.jpg>

as soon as possible - management of the condition is focused on dietary changes, maintenance of an ideal body weight, and strict attention to the exercise regimen. Reduction of carbohydrate intake and provision of energy in the form of fat are the fundamentals of dietary management, and can be achieved with commercial diets as well as directed supplementation. The general recommendation is to provide <10% of the digestible energy in the form of nonstructural carbohydrates, and 15% to 20% as fat.¹⁴ Several appropriate commercial diets are available; most notably Re-Leve® (manufactured by KER in the United States) and Empower® or XTN® (Nutrena Feeds), which is available in Canada. The difference in nutrient distribution between a conventional sweet feed and the Re-Leve® product is demonstrated in Figure 2. If commercial feeds are not an option, fat can be provided in the form of rice bran or vegetable oils fed on a small amount of a palatable feed. Common recommendations for oil feeding specify up to 2 cups/day split into 2 or more feedings; owners should start with small amounts to accustom their horses to the taste and avoid feed refusal. Fat supplementation in the form of rice bran or oils may be insufficient to provide adequate caloric intake to high-performing horses.¹⁴

Regular exercise and avoidance of periods of inactivity are required to manage horses with PSSM. Pasture turnout is ideal and stall rest should be limited to <12 hours per day.¹⁴ Owners should avoid sudden changes to their horse's exercise regimen, such as long trail rides without preparation, or participation in riding clinics without adequate conditioning, and should pay close attention to the fitness level of performance horses. Avoiding stressful events such as long trailer rides and sudden changes to the herd structure are also recommended. Managing a horse with PSSM is a life-long commitment; as a result, owner education is vitally important to maintain client satisfaction and to

maximize the quality of life for the horse. In one study, all horses with owners who followed the dietary and exercise recommendations demonstrated improvement in their clinical signs, while failures in reducing the frequency and/or severity of PSSM episodes were observed among horses not managed according to the recommendations.¹⁵

Recurrent exertional rhabdomyolysis

Recurrent exertional rhabdomyolysis (RER) is a condition that presents a similar clinical picture to PSSM and found mainly in Thoroughbred and Standardbred racehorses. Rather than a carbohydrate disorder, it is suspected that the underlying defect is a disorder of intracellular calcium regulation and a familial basis with dominant inheritance has been suggested.^{16,17} Management of RER is similar to PSSM in terms of diet and exercise; in addition, medications can help to reduce the frequency and severity of episodes in affected horses.

Episodes of rhabdomyolysis in horses affected by RER may be related to the stress of training and racing. Young horses, particularly fillies, as well as horses with a nervous disposition may be at higher risk of demonstrating clinical signs.¹⁸ High-grain rations and certain training strategies were also identified as additional risk factors. As with PSSM, other potential causes of repeated rhabdomyolysis, such as lameness, should always be ruled out in horses suspected to be suffering from RER. The diagnostic approach is similar to PSSM; currently, exercise testing and muscle biopsy are the most promising tests. Characteristically, muscle biopsies reveal centrally located muscle fibre nuclei (as opposed to nuclei located underneath the cell membrane in normal horses) and moderate PAS staining for glycogen.¹⁹

Recommendations for the management of horses affected by RER include a reduction of the carbohydrate portion of the diet - <20% of the digestible energy should be provided in the form of nonstructural carbohydrates - and an increase in the fat portion to 20%-25% of digestible energy. Commercially available diets such as the ones described in the section on PSSM are also recommended for horses with RER. A regular exercise regimen and a reduction in stress are essential. The latter may be achieved by standardizing the daily routine of the horse, feeding and exercising affected horses before their barnmates, and avoiding sudden changes to the exercise regimen.²⁰ Low doses of sedatives (eg, acepromazine) prior to exercise may also be useful to reduce stress in affected horses; however, the safety of both horse and rider should be considered foremost when using this approach.

Dantrolene and phenytoin have been investigated to control episodes of rhabdomyolysis in horses with RER. Dantrolene (2-4 mg/kg orally, 1-hour before exercise) is effective in suppressing calcium release from

the sarcoplasmic reticulum; it has been demonstrated to prevent clinical episodes of rhabdomyolysis, and to reduce the increase of CK with exercise in Thoroughbred racehorses.²¹ Phenytoin has primarily been evaluated for use in horses with hyperkalemic periodic paralysis, but was also found to alter *in vitro* muscular twitch characteristics in horses with chronic intermittent rhabdomyolysis.²² Phenytoin dosages of 1.4–2.7 mg/kg orally twice daily with a monitoring of serum concentrations to maintain serum levels between 8–12 g/mL are recommended.²²

Nonexertional rhabdomyolyses

Nonexertional rhabdomyolyses occur without exercise and are associated with inflammatory, immune-mediated, nutritional, toxic, and metabolic conditions. Another group of these rhabdomyolyses is associated with general anesthesia and includes malignant hyperthermia. Nutritional rhabdomyolysis and metabolic conditions are covered in this issue; the discussion will continue in a subsequent issue.

Nutritional rhabdomyolysis

Nutritional rhabdomyolysis, also known as nutritional muscular dystrophy or white-muscle disease, is a relatively uncommon condition seen primarily in foals and weanlings; it is similar to the syndrome observed in calves and other species. Selenium and, in some cases, vitamin E deficiency are often implicated as a cause of this noninflammatory, degenerative disorder, but cannot be proven in all affected animals.²³ Conversely, not all selenium-deficient animals are affected by the disorder, and other factors including prolonged labour, exercise, and stress are thought to contribute.²⁴ Selenium is an essential component of selenoproteins (eg, glutathione peroxidase), and acts synergistically with vitamin E in the defense against radical-induced peroxidative damage. Two forms are recognized: an acute form of the disease affects the myocardium and frequently results in death, and a subacute form causes more generalized myopathy and dysphagia.²⁴ Nutritional myodegeneration as a cause of dysphagia has been reported in adult horses, and is characterized by painful swelling and edema primarily of the masseter muscles.^{25,26}

Clinical signs in affected foals generally include weakness, firm and painful musculature, lameness, failure to suckle, and recumbency. Abnormal head carriage is common and is caused by weakness of the neck musculature. Respiratory difficulty, cardiac murmurs, and illthrift may also be observed. Foals affected at birth are at risk for failure of passive transfer and sepsis as complicating conditions; aspiration pneumonia is also common. Serum chemistry findings consistent with rhabdomyolysis, and detection of low whole-blood selenium concentrations, glutathione peroxidase activity, and/or serum vitamin E concentrations are the clinical

signs confirming the diagnosis. Liver concentrations of vitamin E and selenium are also useful diagnostically in cases of acute death with a suspected cause of white-muscle disease. Muscle tissues demonstrate characteristic lesions of pale streaking, and histopathological evidence of hyaline degeneration and muscle fibre fragmentation. Gross myoglobinuria is uncommon in affected foals.

Differential diagnoses, depending on the predominant presenting clinical signs, include sepsis, colic, tetanus, botulism, neonatal isoerythrolysis, neurologic diseases, septic polyarthritis, and other causes of lameness.^{23,24} Treatment is supportive, with a correction of vitamin E and selenium status; however, advanced cases are reported to respond poorly to therapy and, on humane grounds, euthanasia may be considered. Exercise restriction is imperative, but muscle fibrosis may result in permanent deficits in surviving animals. Preventive measures are recommended in high-risk areas, including the determination of herd whole-blood selenium status in broodmares during their last trimester followed by supplementation and, if necessary, treatment of foals at birth.²⁴ Due to the relatively small margin of safety in selenium supplementation, addition of selenium to the diet should always be based on whole-blood selenium testing. Postpartum treatment of foals, although effective in preventing the juvenile form of disease, does not eliminate the risk of disease developing *in utero*, if the dam is selenium deficient.

Metabolic causes

Glycogen-branching enzyme deficiency (GBED) in horses is a glycogen-storage disease of Quarter Horses and related bloodlines that was first described in 2001.²⁷ The cause is a nonsense mutation in codon 34 of the GBE1 gene that has autosomal recessive inheritance and results in termination of protein synthesis and the absence of a functional glycogen-branching enzyme.²⁸ The disease has similarities to a glycogen-storage disorder in humans; it is characterized by progressive myonecrosis with an early onset of disease at, or soon after, birth. Clinical signs are variable and include abortion or premature birth, inability of foals to stand and failure to suckle, contracted tendons, lethargy, hypothermia and hypoglycemia, as well as seizures and cardiac or respiratory failure. Temporary improvement of sick foals treated with aggressive supportive care has been reported; to date, however, all known cases have died or were euthanized due to recurrence of clinical signs by 18 weeks of age.²⁸ Reports based on an evaluation of samples obtained from registered Quarter Horses and Paints suggested heterozygote carrier frequencies of 8.3% and 7.1%, respectively.²⁹ Genetic testing for the disorder is available at the University of California–Davis,³⁰ and counselling should be given to breeders about the implications of breeding carrier horses.

Summary

Rhabdomyolysis remains an important cause of morbidity and mortality in horses. Recent advances in identifying underlying myopathies, some of which are now known to be genetically determined, have helped to elucidate the pathophysiology of this group of disorders and to develop more specific treatment and management recommendations. Horse owners and veterinarians are urged to pursue a thorough diagnostic testing of horses with rhabdomyolysis (especially if a recurrent problem is present) to optimize management and, potentially, make important breeding decisions concerning affected horses.

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San Diego, California

CONTACT: David Foley

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Dr. Lohmann has stated that she has no disclosures to announce in association with the contents of this issue.

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This publication is made possible by an educational grant from

Schering-Plough Canada Inc.

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