

A Review of the Diagnosis and Treatment of Rhabdomyolysis in Foals

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Polysaccharide storage myopathy and glycogen branching enzyme deficiency are emerging causes of rhabdomyolysis that can be diagnosed by muscle biopsy. In general, treatment of rhabdomyolysis is aimed at decreasing pain, restoring fluid and electrolyte balance, preventing myoglobinuric renal failure, and where possible, eliminating the inciting cause. Author's address: Department of Clinical and Population Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, MN 55108. © 2002 AAEP.

1. Introduction

Nutritional myodegeneration is a well-recognized cause of rhabdomyolysis in foals.¹ Recently, however, several new causes of rhabdomyolysis in foals have been identified. The purpose of this review is to provide an update on the clinical presentation, clinical pathology, diagnosis, and treatment of common causes of rhabdomyolysis in foals.

2. Clinical Pathology

A diagnosis of rhabdomyolysis is usually made by measuring the activity of the enzymes creatine kinase (CK), lactate dehydrogenase (LDH), and aspartate transaminase (AST) in serum.¹ Serum CK is released by degenerating striated muscle cells and rapidly increases in serum to peak 4–6 h after muscle damage. CK activity also declines rapidly if muscle necrosis has ceased, with a return to normal values within 3–7 days, depending on the original extent of muscle necrosis. Thus, high serum CK activity indicates acute muscle degeneration, and persistently elevated serum CK activity over time indicates ongoing rhabdomyolysis. LDH and AST activity in serum may also indicate muscle necrosis;

however, these enzymes are not specific for muscle damage, because elevations also occur with liver necrosis. Equine biochemistry profiles should include CK, AST, γ glutamyl transferase (GGT), and sorbitol dehydrogenase (SDH) activities to differentiate between muscle and liver necrosis. LDH peaks about 12 h after muscle damage and takes 7–10 days to clear from serum, whereas AST peaks 24–48 h after muscle damage and returns to normal in 5–14 days depending on the extent of muscle necrosis. Thus, in the absence of liver disease, high AST is an indicator of chronic muscle necrosis.

Skeletal muscle represents the largest intracellular fluid compartment in the body. Severe rhabdomyolysis produces disruption of the barrier between extracellular and intracellular compartments, thereby significantly altering the electrolyte composition of both compartments. Serum sodium, chloride, calcium, and extracellular fluid move down a concentration gradient into damaged muscles, whereas potassium, phosphorus, and myoglobin move from damaged muscle cells into the blood stream. Thus, common findings on biochemistry profiles in rhabdomyolysis include high total pro-

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tein, hyponatremia, hypochloremia, hypocalcemia, hyperkalemia, and hyperphosphatemia.² Myoglobin released into the blood stream is filtered through the kidneys. Uptake of myoglobin by renal tubules can impair renal function and result in elevations in serum creatinine and blood urea nitrogen. Serial determination of creatinine is therefore indicated with rhabdomyolysis.

3. Diagnosis

A serum chemistry profile provides information on the severity and likely time of occurrence of muscle necrosis but does not provide a specific diagnosis of the cause of the rhabdomyolysis. Other diagnostic tests that are helpful in assessing foals with rhabdomyolysis and determining potential causes include the following:

- CBC for identification of associated infections such as sepsis, pneumonia, and myositis
- Thoracic radiographs or ultrasound to identify bronchopneumonia or aspiration pneumonia
- Arterial blood gas analysis in neonates for evidence of asphyxia and hypoxia³
- Whole blood selenium concentrations and serum vitamin E concentrations
- Evaluation of pastures for toxic plants such as rayless goldenrod or white snake root
- Muscle biopsy and histopathological evaluation: a muscle biopsy to determine the cause of rhabdomyolysis is indicated when whole blood selenium and serum vitamin E concentrations are normal. The semitendinosus muscle is often the most accessible muscle to evaluate in foals with rhabdomyolysis. After sedation, sterile preparation of the skin, and subcutaneous lidocaine injection, a 4-cm incision is made through skin and fascia. The fascia is undermined, and two 3-cm-long incisions are made 2-cm apart in a fashion that is parallel to the length of the muscle fibers. The tissue is grasped with forceps in one corner only, and the parallel incisions are transected dorsally. The biopsy is excised at a depth of 1.5 cm and then transected ventrally. A thorough subcutaneous layer of absorbable suture and skin staples work well to avoid dehiscence. Muscle tissue should be placed in saline-moistened gauze and kept refrigerated until it is delivered within 24 h to a specialized laboratory.

Differential diagnoses for rhabdomyolysis in foals include birth hypoxia, fulminant sepsis, clostridial myositis, nutritional myodegeneration, polysaccharide storage myopathy, and glycogen branching enzyme deficiency in Quarter Horse-related foals. In a few weanling foals, pasture myopathies of unknown etiology have been observed in the midwestern United States that affected primarily postural and respiratory muscles.

4. Treatment

Foals with rhabdomyolysis should be housed in a clean, deeply bedded stall. The ability of the foal to stand and nurse should be assessed, and assistance to rise and suckle should be provided if necessary. Foals should not be left for more than 1 h in one position. Enteral or parenteral nutrition should be considered if foals are unable to suckle adequate amounts of mare's milk, especially if any degree of dysphagia is suspected. Many foals with rhabdomyolysis develop pneumonia as a result of inhalation of pathogens during recumbency, aspiration of milk, weakness of respiratory muscles, and possibly immunosuppression.^{1,2} Administration of antibiotics to help combat secondary pneumonia is often warranted. Nonsteroidal anti-inflammatory medication such as ketoprofen or flunixin meglumine can be administered to combat pain and inflammation. The degree of renal compromise should be assessed before administration of these potentially nephrotoxic drugs. Fluid and electrolyte abnormalities should be assessed and corrected. Hyperkalemia (>5.5 mEq/l) may be an immediate life-threatening situation in affected foals. Although IV dextrose, bicarbonate, and insulin are traditionally administered to treat hyperkalemia, they may be ineffective in severe rhabdomyolysis because of insufficient intact muscle mass to absorb potassium from the blood. In such cases, mineralocorticoids may be used.² If the foal is hyponatremic, hypertonic saline may be helpful to restore electrolyte balance. If ionized calcium is low, 10% calcium borogluconate (at 2 ml/kg, IV) can be administered slowly, mixed with 0.9% saline.⁴ The minimum amount required to maintain low normal ionized calcium concentrations should be given, because excessive administration will exacerbate calcium deposition in skeletal muscle. Volume overloading with IV fluids should be avoided in foals with rhabdomyolysis because they tend to retain fluid during the first 48 h of muscle necrosis.² If serum creatinine is elevated and the foal is anuric, dobutamine (2–10 µg/kg/min) or dopamine (2–5 µg/kg/min) as an IV infusion may be beneficial.⁴ Acidic urine exacerbates tubular damage by myoglobin, and urine pH is often acidic in foals. Alkalinization of the urine by administering IV sodium bicarbonate may be indicated in foals with visible myoglobinuria and acidic urine.

5. Nutritional Myodegeneration (White Muscle Disease)

Nutritional myodegeneration (NMD) should be suspected in all foals with signs of muscle stiffness and abnormal elevation in serum CK and AST activities, because it is one of the most common causes of acute muscle necrosis in young, rapidly growing foals.¹ Firm painful hindlimb, lumbar, and neck muscles with progressive muscular weakness, stiffness, trembling, and recumbency are common clinical signs. Pneumonia as a result of immunosuppression, dysphagia, and aspiration is a frequent se-

quela. In some foals, dysphagia may be the only initial presenting sign. A rapid, irregular heart-beat, profound weakness, recumbency, and sudden death occur when cardiac muscle is involved.⁵ Serum CK activity can be markedly elevated with NMD and will decline rapidly with treatment. For example, in one foal with NMD, CK declined over 5 days from 490,000 to 955 U/l.²

NMD results from a dietary deficiency of selenium and/or vitamin E in gestating dams.^{5,6} Selenium deficiency seems to be the most important contributor to muscle necrosis based on prophylaxis and response to treatment with selenium alone.¹ A definitive diagnosis of NMD is established by determining whole blood selenium (normal, 0.07 to >0.1 ppm) and plasma vitamin E concentrations (normal, >1.1–2.0 ppm).¹ Vitamin E deteriorates rapidly in plasma samples, so samples should be stored on ice immediately post-collection, protected from light by wrapping in tin foil, and stored frozen (–21°F, –70°C) if analysis is to be delayed. Selenium-dependent glutathione peroxidase (GSH-Px) formed in the red cells during erythropoiesis also provides an index of whole body selenium status. Adequate GSH-Px activities are greater than 20–50 units/mg hemoglobin/min in horses.

In addition to the considerations for treating rhabdomyolysis outlined in Section 4, foals with NMD should receive injectable selenium products IM at a selenium dose of 0.055–0.067 mg/kg (2.5–3 mg/45 kg) body weight.¹ Absorption and distribution of injectable selenium occurs rapidly and may account for the rapid improvement in clinical signs seen in reversible cases. Injection site reactions are common, so dilution with sterile saline and injecting the pectoral muscles in two sites is recommended. Injection of cervical muscles is not recommended because injection reactions in the neck will decrease the foal's ability to suckle. Injectable selenium contains 50 mg/ml (68 IU) of vitamin E as *dl*- α -tocopheryl acetate and is insufficient for vitamin E supplementation. Injectable vitamin E products are now available which contain 300 IU vitamin E/ml as *d*- α -tocopherol.^a Administration of these products increases the tissue and/or plasma level of vitamin E for approximately 3 wk. Oral α -tocopherol is now available for all species and contains 500 IU vitamin E/ml. The recommended dosage of this product is 1–3 IU/lb body weight.

The prognosis for foals with NMD is guarded for the first 1–2 days of treatment until foals show an improvement in muscle weakness and can stand. Foals that remain recumbent for 3–5 days without significant clinical improvement have a poor prognosis. If myocardial involvement is present it is usually extensive and invariably fatal.

Other foals on the farm should receive an injection of selenium/vitamin E. In addition, lactating and gestating dams on the farm should be supplemented orally with 1 mg of selenium per day.⁷ In high-risk areas, blood samples for selenium should be taken

every 60–90 days to determine selenium status in susceptible animals and every 6–12 mo to monitor supplementation. On the basis of these assessments, adjustments to the rate or extent of selenium supplementation may be made.¹ Feeding animals properly prepared and stored hay and grain or allowing them access to high-quality green forage should ensure adequate vitamin E intake. The precise interrelationships between selenium, vitamin E, other metabolic factors, and triggering mechanisms in NMD are not fully understood because many animals deficient in selenium and/or vitamin E have no evidence of muscle disease.

6. Polysaccharide Storage Myopathy

Polysaccharide storage myopathy (PSSM) is a common muscle disease in Quarter Horse-related breeds.^{8,9} PSSM is an inherited trait characterized by enhanced insulin sensitivity and the accumulation of glycogen and an abnormal polysaccharide in skeletal muscle fibers.^{8,10,11} Clinical signs of PSSM are usually seen in adult horses at the commencement of training or when exercise resumes after a period of rest and include muscle stiffness, pain, and reluctance to exercise.⁹ Serum CK activity may be elevated at rest in PSSM horses and may increase up to 80,000 IU/l after a 15-min submaximal exercise test. Persistent subclinical elevations in CK are common in unfit adult horses with PSSM.⁹ Two recent papers suggest that PSSM may also be an important cause of rhabdomyolysis in foals.^{12,13}

Four foals out of PSSM lineage were followed from birth to 3 yr of age.¹³ Three of the foals developed subclinical elevations of CK as great as 10,000 U/l as early as 1 mo of age. When foals developed strangles, CK activity was as high as 35,000 U/l. Foals showed enhanced insulin sensitivity when first tested at 6 mo of age. Turn-out of foals on pasture for 24 h/day resulted in normal serum CK responses to exercise, whereas stall confinement caused significant elevations in CK with treadmill exercise. Although serum CK was elevated at an early age, the accumulation of abnormal polysaccharide in skeletal muscle did not occur in these foals until 7–18 mo of age. This paper confirmed a heritable basis for PSSM and suggests that abnormal polysaccharide accumulation in muscle is a secondary feature of the disease. Thus, a definitive diagnosis of PSSM by muscle biopsy may not be possible until 2–3 yr of age.

In a second report, severe rhabdomyolysis associated with PSSM was identified in 3-mo-old and 6-mo-old Quarter Horse foals.¹² Both foals had concurrent bacterial pneumonia and developed muscle stiffness, weakness, fasciculations, and difficulty rising. Serum CK activity was as high as 236,600 U/l, and alterations in electrolytes and creatinine concentrations described in Section 3 were present. Muscle biopsies submitted to the University of Minnesota showed small amounts of abnormal polysaccharide in scattered muscle fibers consistent with

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PSSM. In addition, a biopsy of one of the dams was submitted and found to be positive for PSSM. Similar to adult horses with PSSM, serum CK activity in both foals was persistently elevated above the normal range for more than 10 days. Foals were treated as described in Section 4 and recovered within 10–14 days. Recommendations for management included daily pasture turn-out, eliminating sweet feed from the diet, and providing a concentrate ration containing 6% fat together with a balanced vitamin/mineral supplement and grass hay. The 3-mo-old foal did well with these management changes. The owner of the 6-mo-old foal elected not to follow the recommendations, and this foal was euthanized because of a second severe episode of rhabdomyolysis. A full sibling developed severe rhabdomyolysis the following year.

A diagnosis of PSSM is established in a muscle biopsy by the presence of normal to increased period acid schiffs (PAS) background staining for glycogen and PAS positive inclusions within muscle fibers.⁸ Because the accumulation of abnormal polysaccharide is a variable finding at a young age, muscle biopsy of the dam and sire, if possible, may facilitate the diagnosis. Breeding horses with PSSM is not recommended because of the evidence supporting inheritance of the trait, the severity of clinical signs in foals, and the high likelihood of recurrence of rhabdomyolysis in affected animals.^{11,13}

Management of foals with PSSM should include minimal box stall confinement, access to as much turn-out as possible, and a diet that is low in starch and provides energy in the form of a fat supplement. A low-starch, high-fat commercial pelleted diet called "Re-leve" has recently been developed that, when combined with grass/alfalfa hay, provides a balanced ration for growing Quarter Horses.^b

7. Glycogen Branching Enzyme Deficiency

Glycogen branching enzyme deficiency (GBED) is a newly recognized disorder causing muscle weakness in Quarter Horse-related breeds.¹⁴ It represents a separate glycogen storage disorder from PSSM. The clinical presentation of this disease is variable. Late-term abortion or stillbirth of affected foals has been reported.¹⁵ Affected foals are often weak and hypothermic at birth but respond when bottle-fed or assisted to nurse. Foals with GBED may develop intermittent hypoglycemia, weakness, and seizures if they do not nurse regularly. Flexural deformities of all limbs that respond to oxytetracycline or splinting are common.

Moderate tachypnea may be present; however, one neonate with GBED developed respiratory failure requiring mechanical ventilation. Owners may note that GBED foals are less active than other foals, and progressive muscular weakness may be observed. Sudden collapse and death has occurred in several foals while turned-out on pasture. Difficulty moving from lateral to sternal recumbency because of muscular weakness can be a presenting

sign in some foals. In contrast to NMD and PSSM, GBED foals do not develop palpably firm painful muscles. Despite aggressive treatment in neonatal intensive care unit (NICU) facilities, the disorder in all known cases has been fatal by 8 wk of age.

Clinicopathological features of GBED include leukopenia, intermittent hypoglycemia, and persistently high serum CK, AST, and GGT activities. Serum CK activity is not usually greater than 30,000 U/l. A diagnosis is easily missed because gross postmortem changes are not evident, and routine hematoxylin and eosin (H&E) stains of tissues may be normal. A diagnosis of GBED is initially made from PAS stains of skeletal \pm cardiac muscle. A lack of background PAS staining for normal glycogen and a variable amount of abnormal PAS positive globular or crystalline intracellular inclusions in skeletal muscle and cardiac tissues, including Purkinje fibers, are characteristic for GBED. Globular basophilic inclusions or eosinophilic crystalline material may or may not be present in H&E stains. The activity of the glycogen branching enzyme, which is essential for the formation of normal glycogen, is markedly reduced in tissues from affected foals, and their dams usually display 50% normal serum GBE activity. In contrast, horses with PSSM do not have a reduction in GBE activity. GBE activity can be determined in whole blood if special arrangements are made with the laboratory, and samples arrive within 24 h of drawing the blood.

A diagnosis of GBED should be suspected in foals from Quarter Horse-related breeds that present with weakness, contracture of all limbs at birth, and have a combination of persistent hypoglycemia, leukopenia, and elevated CK (1000–15,000 U/l), AST, and GGT. Confirmation requires submission of frozen skeletal muscle biopsies, at necropsy, cardiac tissue for histopathological, and biochemical examination. GBED represents a fatal autosomal recessive form of a glycogen storage disease in Quarter Horse-related breeds. A genetic test for this disease is not yet available. Breeding the dam of an affected foal to the same stallion is likely to result in a 25% chance of producing another affected foal.

8. Summary

Rhabdomyolysis is a common occurrence in young foals in response to hypoxia, nutritional myodegeneration (NMD), polysaccharide storage myopathy (PSSM), and glycogen branching enzyme deficiency (GBED). Clinicopathological features of NMD and PSSM include weakness, muscle stiffness, high serum CK and AST activity, hyponatremia, hypochloremia, hypocalcemia, hyperkalemia, hyperphosphatemia, and myoglobinuria. Persistent elevation in serum CK activity in the face of normal blood selenium and vitamin E concentrations warrant a muscle biopsy to establish a diagnosis. In Quarter Horse-related breeds, GBED is a distinct systemic glycogen storage disorder that presents in a variety of fashions including stillbirth, weakness, respira-

tory insufficiency, flexural limb deformities, or sudden death. Both PSSM and GBED seem to be inherited.

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^aVital E; Schering-Plough Animal Health, Kenilworth, NJ 07033.

^bRe-leve; Hallway Feeds, Lexington, KY 40508.