RECURRENT EXERTIONAL RHABDOMYOLYSIS OF THOROUGHBREDS

Recurrent exertional rhabdomyolysis (RER) may occur in up to 5% of racing thoroughbreds. Pedigree analysis has shown a probable autosomal dominant mode of inheritance with variable expression. The syndrome is characterized by mild, moderate or severe rhabdomyolysis that begins shortly after the onset of aerobic exercise. Muscle cramping is usually accompanied by tachycardia, tachypnea, sweating, reluctance to move, and occasionally recumbency.

Laboratory diagnosis is similar to other causes of rhabdomyolysis. Since the rhabdomyolysis occurs early after the onset of exercise, systemic dehydration and acidosis rarely occur. Thoroughbreds with RER will often have elevations in CK that are not associated with any clinical signs. This subclinical manifestation of the disease can lead to CK activities as high as 10,000 U/L. Biopsy specimens show an increased number of centrally located nuclei within the muscle fibers. In vitro contracture studies on intercostal muscle fibers show an increased sensitivity to potassium, caffeine and halothane. These horses also have quicker times to 50% contraction and 90% relaxation compared to normal horses and horses with other underlying muscle diseases.

The disease is most commonly seen in young thoroughbred fillies with nervous temperaments. Stress is thought to be one of the most important predisposing factors. High carbohydrate diets may lead to higher CK activity. Horses are more likely to develop clinical signs if they are exercised at a medium gallop or a trot than if they are racing or at a full gallop. Lameness, inclement weather and time of year have also been cited as possible predisposing causes.

Treatment of RER is aimed at decreasing the incidence of the episodes by changes in management including a high-fat, low-starch diet, changes in exercise and turnout regimens, and treatment of underlying lameness. Dantrolene at 4 mg/kg to fasted horses 90 minutes prior to exercise, has been shown to lower post-exercise serum CK activities. For horses with severe episodes, treatment of RER should be the same as for other causes of acute rhabdomyolysis and should include management of pain, correction of dehydration, muscle relaxants, and management of the recumbent horse, if necessary.

POLYSACCHARIDE STORAGE MYOPATHY

Polysaccharide Storage Myopathy (PSSM) is a heritable form of recurrent rhabdomyolysis that has been documented in Quarter Horses, Quarter Horse crosses and related stock-type breeds, such as Appaloosas and Paint Horses, Draft horse and Draft horse crosses. These horses exhibit recurrent episodes of rhabdomyolysis, usually following mild periods of exercise. The severity of the episode is not always correlated with the degree of increase in muscle enzymes, as some horses appear to be more tolerant than others. Some horses have persistent elevations of CK, even between clinical episodes.

Horses with PSSM have an abnormal periodic acid-Schiff positive (PAS+) polysaccharide accumulated within the muscle cells on biopsy specimens. On the metabolic
level, PSSM horses exhibit increased muscle glycogen concentrations, increased glycogen utilization rates, and increased glucose clearance rates characterized by a shorter glucose half-life, lower baseline insulin, and lower mean insulin concentration and an increased sensitivity to insulin.

The diagnosis of PSSM is initially made based on the history of recurrent episodes of rhabdomyolysis, appropriate parentage, and an exercise tolerance test. The diagnosis can then be confirmed with a muscle biopsy. A genetic test is also available for PSSM Type I, which is a mutation in the GYS1 gene and accounts for up to 90% of the disease in some horse breeds.

Treatment of acute episodes of PSSM is the same as for any type of rhabdomyolysis. Long term management involves minimization of stress, dietary changes, regular turnout and regular exercise routines. Exercise will decrease the muscle sensitivity to insulin, burn off the stored glycogen, and increase the utilization of fat for fuel, rather than glucose. A low carbohydrate diet is essential. Extra calories are provided by adding corn oil or rice bran. A mineral supplement should be added for a balanced ration. Specific diets, such as Re-Leve®, have been developed. Vitamin E and selenium supplementation are also recommended. Although there is no cure for PSSM, >95% of horses that are treated with the recommended dietary and exercise changes will improve.

GLYCOGEN BRANCHING ENZYME DEFICIENCY

Glycogen branching enzyme deficiency is a fatal autosomal-recessive disease of Quarter Horses and Paint Horses caused by a mutation of the glycogen branching enzyme 1 (GBE1) gene which drastically decreases the amount of GBE protein in homozygotes. Carriers of GBED trace back to King P234 in most cases, as well as his sire, Zantanon. The majority of Quarter Horses, however, are descendants of these two stallions so pedigree analysis is not very helpful. Approximately 8% of Quarter Horses and Paint Horses are carriers of GBED. The incidence of GBED in fetuses from 2nd and 3rd trimester abortions is as high as 2 - 4% based on specimens submitted to 2 diagnostic laboratories. The incidence overall may be higher due to the similarity of clinical signs with many neonatal diseases and the current lack of genetic testing of stillborn foals and aborted feti.

Affected foals have extremely low glycogen branching enzyme activity, therefore, diseased foals cannot store and mobilize glycogen to maintain normal glucose homeostasis. The most common clinical signs of GBED include abortion of the affected fetus and stillbirths. Those that survive to parturition are often born weak and hypoglycemic/hypothermic but improve with bottle feeding. Other clinical presentations include progressive muscle weakness, inability to rise, collapse, seizures, flexural limb deformities, respiratory failure, and sudden death. Common laboratory findings include leukopenia, intermittent hypoglycemia, and moderate elevations of serum CK, AST, and GGT activities.

Diagnosis is based on genetic testing of mane or tail hair, or through muscle biopsy. Histologically, there are globules of abnormal polysaccharide with no normal background pink staining in the GBED biopsy. Nursing care has prolonged life in affected foals, but unfortunately there is no curative treatment.

MALIGNANT HYPERThERMIA

Malignant hyperthermia (MH) is classified as a pharmacogenetic disorder that is often fatal in affected horses. These horses may have no predisposing clinical signs and the disease does not manifest itself until the horse is anesthetized with volatile anesthetics (i.e. halothane) or
neuromuscular blockers (i.e. succinylcholine). The underlying pathology is a mutation in the ryanodine receptor type 1 (RyR1) gene, the gene that controls the release of calcium from the sarcoplasmic reticulum in skeletal muscle and is therefore a key element in excitation-contraction coupling. Horses that are never exposed to the triggering factors may never be diagnosed. Some case reports have documented MH episodes in horses with other underlying myopathies, such as PSSM. Horses that have mutations in both the GYS1 and RYR1 genes have a more severe manifestation of these diseases.

Clinical signs in affected horses can occur at any time during anesthesia or in the immediate postoperative period. These usually include hyperthermia (102.2 to >107.6°F), muscular rigidity, profuse sweating, tachycardia, tachypnea, retraction of the eye with protrusion of the third eyelid, trismus, and flared nostrils. Hematological analyses can include hypercapnia, metabolic acidosis, hypertension, hypocalcemia, hypomagnesemia, hyperphosphatemia, hyperkalemia, and hyperglycemia. CK, AST, and LDH activities are usually high, and myoglobinuria may be present. In a retrospective study of 18 cases of MH in the horse, the mortality rate was 36%. Detection of the mutated gene is done by a PCR test that is now available through the Neuromuscular Disease Laboratory at UC, Davis.

Treatment should be instituted as soon as clinical signs are noted. If possible, the inhalation anesthetic should be discontinued. Injectable anesthetics can be used as an alternative if the horse cannot be immediately recovered. Oxygen should be continued during recovery. An attempt should be made to decrease the body temperature through the use of ice, alcohol baths and cold intravenous fluids. Electrolyte abnormalities should be corrected with the IV fluids, and sodium bicarbonate can be administered to correct the metabolic acidosis. Muscle relaxants such as diazepam, glycercyl guaiacolate (GG), α-2 agonists and opioids have also been recommended to reduce muscle spasm and provide analgesia, however they may prolong anesthesia and/or cause ataxia. NSAIDs are often given for analgesia, but they should be used with caution due to potential renal injury if myoglobinuria is present. Acepromazine may be used since it causes minimal ataxia and can act as a vasodilator to improve circulation in the muscles. Dantrolene sodium has also been recommended for treatment of MH. An intravenous loading dose of 1.9 mg/kg followed by oral or intragastric doses of 2.5 mg/kg every hour has been suggested.

SEASONAL PASTURE MYOPATHY

SPM or Atypical Myopathy is a devastating disease that can be fatal in approximately 90% of cases. A toxin in the seeds of the box elder tree (Acer negundo) has just been discovered to cause SPM in North America. Ingestion of sufficient quantities of box elder seeds results in breakdown of respiratory, postural, and cardiac muscles. A similar disease has been noted in Europe, however the link between box elder seeds and the development of disease has not been fully investigated. Aside from exposure to these seeds, other risk factors include other affected pasturemates; being pastured for over 12 hours daily; the fall season; lack of supplemental hay while horses are on pasture; sparse pasture with short grass; the presence of trees with dead wood on the ground; heavy wind or rain in the week preceding clinical signs; and introduction of a horse onto a pasture for its first season, such as a young horse or a horse that has recently moved to a farm. Characteristic signs of disease include stiffness, difficulty walking or standing, voiding dark urine, and eventually breathing rapidly and becoming recumbent before death. It is often confused with colic or founder. Treatment requires early diagnosis and intensive care, but is often unsuccessful.
**NUTRITIONAL MYODEGENERATION (WHITE MUSCLE DISEASE)**

Nutritional myodegeneration (NMD) is a common cause of rhabdomyolysis in young, rapidly growing foals. It results from a deficiency in selenium and/or vitamin E in gestating dams. This deficiency is then present in the foals and leads to widespread muscle necrosis and rhabdomyolysis.

The disease can present in two different ways including an acute form involving the heart muscle, and a subacute form involving skeletal muscles with or without cardiac involvement. The acute form usually presents as cardiovascular collapse and death from fatal arrhythmias within hours or days. The subacute form presents as a profound muscle weakness. Foals are unable to stand and nurse. Muscle pain and stiffness are often apparent with palpation along the hind limbs, back and neck. Affected foals may appear spastic or ataxic while walking. Dysphagia is often present and may lead to failure of passive transfer, aspiration pneumonia and starvation.

Diagnosis is based on the appropriate clinical signs and laboratory analysis. Serum CK and AST activities are typically high, with CK values often reaching > 5,000 IU/L. Other biochemical derangements may include azotemia, hyponatremia, hypochloremia, hyperkalemia, myoglobinuria and metabolic acidosis. A respiratory acidosis with hypercapnea may also be present if the ventilatory muscles are involved. Diagnosis is confirmed by measuring whole blood or liver selenium concentrations.

Treatment is often not possible in the acute form of the disease. In the subacute form, it is aimed at supplementing these foals with the necessary Vitamin E and selenium. Injectable vitamin E/selenium products should not be given intravenously due to the high risk of anaphylactic reactions. They should be administered intramuscularly at a dose of 0.6 mg/kg, divided and injected into 2 different sites, preferably the pectoral muscles, as a single treatment. Many of the combination products do not contain sufficient amounts of vitamin E, therefore oral supplementation should be instituted. Supportive care, fluids, electrolyte supplementation, analgesia, plasma transfusions for failure of passive transfer and antibiotic therapy for aspiration pneumonia are also crucial. The prognosis in these cases is always guarded, particularly if the foal becomes unable to rise or develops severe electrolyte abnormalities. Prevention of NMD by supplementation of gestating mares with 1 mg of selenium per day is recommended. Selenium is a proven teratogen in swine, therefore many authors caution against supplementing mares in early pregnancy. If one case is present on the farm, the other mares and foals should be checked for selenium deficiencies and treated as necessary.

**VITAMIN E-DEFICIENT MYOPATHY**

Some horses with clinical signs of EMND and a deficiency in vitamin E are not diagnosed antemortem with EMND because they lack evidence of neurogenic atrophy in the sacrocaudalis dorsalis (SC) muscle. A recent study suggests that many such undiagnosed cases are the result of a specific myogenic presentation of vitamin E deficiency. Muscle a-tocopherol concentrations from affected horses were all low, but serum a-tocopherol concentrations were inconsistently low. The observed generalized weakness in the horses with abnormal mitochondrial stains was suggested to be due to a reversible manifestation of skeletal muscle/mitochondrial oxidative stress associated with vitamin E deficiency. All horses recovered completely after vitamin E therapy. Vitamin E-deficient myopathy could be an entity unto itself or a predecessor to development of EMND, but this distinction was not evaluated in the study as all horses successfully responded to vitamin E therapy, precluding a postmortem examination.
STREPTOCOCCAL ACUTE SEVERE Rhabdomyolysis

Severe acute rhabdomyolysis is a rare but often fatal complication following upper respiratory infection with Streptococcus equi, a β-hemolytic group C streptococcus. Myalgia, myoglobinuria, stiffness, stilted gait most notably of the pelvic limbs, severe swelling and pitting edema of the epaxial and gluteal muscles, and recumbency are common clinical signs. Clinical signs progress rapidly and may result in death despite aggressive antimicrobial, anti-inflammatory, fluid, and supportive therapy. Affected horses have leukocytosis with neutrophilia, and hyperfibrinogemia. The serum CK activity is markedly elevated (>100,000 IU/L). Myonecrosis of up to 75% of myofibers with histiocytic infiltration is the most common pathological alteration in muscle biopsy samples. Staining with Lancefield group C carbohydrate-specific and S. equi M protein (SeM) specific antisera have revealed numerous cocci in skeletal muscle. In addition, affected horses have elevated serum antibody titers to S. equi myosin binding protein. The pathophysiology of the disease is not fully understood but the presence of streptococcal superantigens may play an important role as described in humans with streptococcal necrotizing myopathy.

INFARCTIVE PURPURA HEMORRHAGICA

Purpura hemorrhagica is a non-contagious disease of horses characterized by vasculitis leading to extensive edema and hemorrhage of the mucosa and subcutaneous tissue. The disease has been recognized as a sequela to infection or exposure to Streptococcus equi, Streptococcus equi zooepidemicus, Rhodococcus equi, Corynebacterium pseudotuberculosis and vaccination against S. equi equi. An infarctive form of purpura hemorrhagica occurs in young to middle aged horses. Clinical signs develop acutely within 2–4 weeks following a respiratory infection and include muscle swelling and stiffness with elevated muscle enzyme activities (CK > 50,000 IU/L and AST > 1000 IU/L); subcutaneous edema of all four limbs, lethargy, anorexia, hemorrhages on mucous membranes, fever and tachycardia. Neutrophilia with left shift, hypoalbuminemia, and abnormal clotting parameters are common. Horses have high titers for antibodies against S. equi M protein by ELISA. Histologically, there is severe, multifocal coagulative necrosis of skeletal muscle. Several other tissues (lungs, liver, intestines) show hemorrhages and leukoclastic vasculitis that progress to infarction. The mortality rate for horses with the infarctive form of purpura hemorrhagica is high.

VIRUS ASSOCIATED MYOPATHY

Breakdown of skeletal and cardiac muscle can also occur in association with viral diseases such as equine influenza and equine infectious anemia. The viral-induced muscle damage is generally part of a larger systemic infection. Equine influenza A2, in particular, has been known to cause severe rhabdomyolosis. Other viruses have slightly different clinical presentations, such as equine herpes virus-1, which has been associated with muscle stiffness and clinical signs similar to exertional rhabdomyolysis.