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J.D. Pagan

EXERTIONAL RHABDOMYOLYSIS IN THE HORSE

STEPHANIE J. VALBERG
Department of Clinical and Population Sciences, College of Veterinary Medicine, University of Minnesota, St Paul, Minnesota, USA

The term "tying-up" has been applied to describe horses that develop firm hard gluteal and lumbar muscles and the inability to move the hind quarters after exercise. Other terms for this syndrome include azoturia, Monday Morning Disease, exertional rhabdomyolysis and chronic intermittent rhabdomyolysis. It has been implied or assumed that all horses which show evidence of muscle pain and cramping following exercise have the same disease. As a result, a great deal of controversy and confusion has developed regarding the cause and approach to treatment of this condition. Exertional rhabdomyolysis likely represents a pathological description of a number of muscle diseases which have common clinical signs. Recently by applying clinical protocols that include muscle biopsies and exercise testing a number of specific disorders have been identified.

Two general syndromes are apparent from a clinical standpoint: 1) sporadic rhabdomyolysis following exercise in horses that have a previous history of satisfactory performance, and 2) recurrent exertional rhabdomyolysis.

Sporadic exertional rhabdomyolysis

CLINICAL SIGNS

Signs of exertional rhabdomyolysis can range in severity from mild stiffness following exercise to recumbency. During exercise, horses develop a short stiff stride, sweat profusely, and have an elevated respiratory rate. Upon stopping horses are reluctant to move, males frequently posture to urinate and in severe cases myoglobinuria may be apparent. Physical examination reveals painful muscle cramps especially in the gluteal area. Scintigraphic evaluation of horses with rhabdomyolysis following exercise shows symmetrical damage to the gluteal, semitendinosus and semimembranosus muscles. Some horses may be extremely painful which could be confused with colic. Muscle pain usually persist for several hours. Endurance horses often show other signs of exhaustion including a rapid heart rate, dehydration, hyperthermia, synchronous diaphragmatic flutter and collapse.

DIAGNOSIS

A diagnosis of exertional rhabdomyolysis is made on the basis of a history of muscle cramping and stiffness following exercise and moderate to marked elevations in serum myoglobin, creatine kinase (CK), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST). These serum proteins are listed in the order of their rate of increase in the blood and in reverse of their rate of clearance from serum.

TREATMENT

The objective of treatment is to relieve anxiety and muscle pain, correct fluid and acid base deficits and prevent renal compromise. The hydration status of horses with myoglobinuria should be assessed immediately. Oral and/or intravenous fluid therapy is a first-order priority in dehydrated horses prior to the administration of nonsteroidal anti-inflammatory drugs (NSAID).

Acepromazine, an alpha-adrenergic antagonist, is helpful in relieving anxiety and may increase muscle blood flow. Its use is contraindicated in dehydrated horses. In extremely painful horses, detomidine provides better sedation and analgesia. Nonsteroidal anti-inflammatory drugs at relatively high doses provide pain relief. Intravenous dimethyl sulfoxide (as a < 20% solution) and corticosteroid administration have also been advocated in the acute stage. Muscle relaxants such as methocarbamol seem to produce variable results.

Rest with hand walking once the initial stiffness has abated is of prime importance. At this time the diet should be changed to good quality hay with little grain supplementation. The amount of rest a horse should receive is controversial. Horses with recurrent problems with rhabdomyolysis appear to benefit from an early return to a regular exercise schedule. Horses that appear to have damaged their muscles from over-exertion may benefit from a longer rest period with regular access to a paddock. Training should be resumed gradually and a regular exercise schedule, which will match the degree of exertion to the horses underlying state of training, should be established. Endurance horses should be encouraged to drink electrolyte supplemented water during an endurance ride and monitored particularly closely during hot humid conditions.

PATHOPHYSIOLOGY OF ACUTE RHABDOMYOLYSIS

The most common cause of exertional rhabdomyolysis is exercise that exceeds the horse's underlying state of training. This includes both exercise at speed as well as endurance riding. Tears in the junctions between intracellular myofilaments (Z lines) are a common cause of post-exercise muscle soreness in humans. The incidence of muscle stiffness and exertional rhabdomyolysis has been observed to increase during

an outbreak of respiratory disease. Both equine herpes virus 1 and equine influenza virus have been implicated as causative agents. Mild muscle stiffness with concurrent viral infections is likely the result of the release of endogenous pyrogens. More severe rhabdomyolysis may be due to exertion during a concurrent systemic infection and/or viral replication in muscle tissue. Since the inciting cause is usually temporary, most horses respond to rest and a gradual increase in training. This may also account for the myriad of treatments guaranteed to cure tying-up in horses.

REPAIR OF SKELETAL MUSCLE

Skeletal muscle shows remarkable ability to regenerate following injury. Following exertional complete repair of muscle tissue is possible within 4 - 8 weeks.

Recurrent exertional rhabdomyolysis

A number of horses, predominantly fillies, will have recurrent episodes of rhabdomyolysis even with light exercise. Recurrent exertional rhabdomyolysis (RER) is seen in many breeds of horses including Quarter Horses, American Paint Horses, Appaloosas, Thoroughbreds, Arabians, Standardbreds and Morgans. A wide variety of causes for RER have been proposed including electrolyte imbalances, hormonal imbalances, lactic acidosis vitamin E and selenium deficiencies. Most recently, however, some specific causes of RER have been identified in the horse. These include a disorder of muscle contractility or excitation contraction-coupling (chronic intermittent rhabdomyolysis) and a disorder in carbohydrate storage and utilization (polysaccharide storage myopathy).

CHRONIC INTERMITTENT RHABDOMYOLYSIS

RER is a common occurrence in Arabian, Standardbred and Thoroughbred horses. It most commonly occurs in young fillies with a nervous disposition. About 5 % of Thoroughbred race horses develop RER during the racing season, often when they trained at a gallop but held back from full racing speeds. Some highly susceptible individuals have repeated episodes resulting in persistent elevations in serum AST and poor performance. Many of these fillies are retired as brood mares. In other susceptible horses, episodes may be very intermittent and as a result the term chronic intermittent rhabdomyolysis has been used to describe this syndrome. Stress and a period of stall rest preceding exercise appear to trigger RER in susceptible horses. Studies of equine lymphocyte antigens provide some support for a familial basis for RER in Standardbred horses and a much higher prevalence of ER has been noted in the offspring of one of two Thoroughbred stallions bred and trained at the same

farm. A diagnosis of chronic intermittent rhabdomyolysis is based on the history and clinical signs as well as documented elevations in serum AST and CK. Muscle biopsy findings in affected horses include varying stages of muscle necrosis and regeneration with centrally located myonuclei.

Lactic acidosis was previously believed to cause RER and many treatments still used today are directed at resolving a lactic acidosis (lactinase, DMG, sodium bicarbonate). Research has shown, however, that RER occurs most commonly with aerobic exercise and that during an episode affected horses have low muscle lactate concentrations and a metabolic alkalosis. In England, a dietary deficiency of sodium or a low calcium: phosphorus ratio based on urine creatinine clearance ratios was suggested to contribute to RER. Subsequent studies showed that many of the Thoroughbred racehorses with chronic intermittent rhabdomyolysis had normal electrolyte ratios. Most recently an abnormality in excitation-contraction coupling has been identified in Standardbred and Thoroughbred horses with RER. The altered relaxation of muscle following a contractile twitch in affected horses suggests that abnormal intracellular calcium regulation is the cause of this form of RER. In addition a recent study showed elevated myoplasmic calcium concentrations in horses with acute RER.

Prevention of further episodes of RER in susceptible horses should include standardized daily routines and an environment that minimizes stress. The diet should be adjusted to include a balanced vitamin and mineral supplement, high quality hay and a minimum of carbohydrates such as grain and sweet feed. Dietary fat supplements may help to maintain weight in nervous fillies without providing excessive carbohydrates. The use of low doses of acepromazine before exercise in excitable horses is believed to help some horses. Daily exercise is essential, whether in the form of turn-out, longeing or riding. In the past, horses have been box stall rested for several weeks following an episode of RER. It is the author's opinion that this is counterproductive and increases the likelihood that the horses will develop RER when put back into training. The initial muscle pain usually subsides within 24 hours of acute RER and daily turn-out in a small paddock can be provided at this time. Subsequently, a gradual return to performance is recommended once serum CK is within normal range. Dantrolene (2mg/kg PO) given 1 hour before exercise is believed to be effective in preventing RER in some horses. Dantrolene is used to prevent malignant hyperthermia in humans and swine by decreasing the release of calcium from the calcium release channel. Phenytoin (1.4-2.7 mg/kg PO BID), has also been advocated as a treatment for horses with RER. Therapeutic levels vary, so oral doses are adjusted by monitoring serum levels to achieve 8 ug/ml and not exceed 12 ug/ml. Phenytoin acts on a number of ion channels within muscle and nerves including sodium and calcium channels. Unfortunately long-term treatment with dantrolene or phenytoin is expensive.

POLYSACCHARIDE STORAGE MYOPATHY (PSSM)

A subset of horses with recurrent exertional rhabdomyolysis (ER) have been found to have a glycogen storage disorder characterized by the accumulation of a nonbioavailable polysaccharide in their muscle. To date Quarter Horses, Paint, Appaloosa, Draft, Draft crossbreds, warmbloods and a few Thoroughbreds have been identified with PSSM. Horses with PSSM often have a calm and sedate demeanor. Most horses have a history of numerous episodes of ER beginning with the commencement of training; however, mildly affected horses have only one or two episodes/year. Exercise intolerance, muscle atrophy, renal failure or respiratory distress are less common presenting complaints. Elevations in muscle enzymes are usually found if blood samples are obtained and muscle enzymes may remain elevated for long periods even when rested. The severity of episodes of rhabdomyolysis can range from mild stiffness to severe pain resembling colic. Several horses have been euthanized due to the severity of muscle damage. A diagnosis is based on examination of muscle biopsies. The distinctive features of these muscle biopsies are subsarcolemmal vacuoles, glycogen storage and abnormal PAS positive inclusions in fast twitch fibers. Muscle glycogen concentrations are often 1.5 - 4 X normal. Serum CK activities are often increased by 1000 U/L or more 4 hours after 15 minutes of exercise at a trot.

While histological and biochemical studies identify PSSM as a glycogen storage disorder, the exact metabolic defect in glycolysis or glycogen synthesis has not been identified. Muscle cramping and damage with exercise has been attributed to the inability of glycolysis to generate ATP for mechanical work and maintenance of chemical gradients. Treatment of horses with polysaccharide storage myopathy is based on increasing the oxidative capacity of skeletal muscle through gradual training and providing a high fat diet. Most PSSM horses have competed successfully as pleasure and hunter horses when their diets are switched to good quality grass hay, no grain or sweet feed and a fat supplement. Rice bran consisting of 20 % fat, corn oil, or spray dried fat supplements can be used. Daily longeing or riding as well as pasture access are essential. Box stall rest for more than 12 hours per day appears to increase the incidence of rhabdomyolysis.

A familial basis for this disorder has been identified in Quarter Horse-related breeds. Currently breeding trials are underway at the University of Minnesota to determine if this is a heritable condition. A few young Quarter Horses (8months-2 yrs) have recently been identified with polysaccharide storage myopathy that developed moderate to severe rhabdomyolysis without any associated exercise. These young halter horses were on a high grain diet and serum CK normalized when switched to a lower carbohydrate ration.

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