Exertional rhabdomyolysis – Keeping up with Evolution

Is it a disease or is it a symptom?

By Susan A. Mende, DVM, Dipl. ACVP

Muscle disease in horses, especially working horses, has been recognized for well over 100 years. The condition termed "Monday Morning Disease" was recognized in horses in the days when horses performed the everyday duties now performed by cars, trucks and tractors. Horses worked long hours, usually six days a week. When given a day of rest on Sunday and provided with a full ration of grain, these horses were prone to massive muscle injury when put in harness on Monday morning. Although it was recognized for years that Monday-morning disease (MMD) involved a high grain ration and lack of exercise, decreasing grain and providing daily exercise were no guarantee that this disorder might not still occur. The recognition that MMD reflects an underlying myopathy rather than being simply a management problem has resulted in a whole new way of looking at horses with muscle disorders (1). But back then, Monday Morning Disease was lumped into a broad category of exertional muscle disorders, medically termed exertional rhabdomyolysis or ER.

Exertional rhabdomyolysis (**ER**) literally means the dissolution of striated muscle with exercise. Over the past century, a number of terms have been used to describe this syndrome including Monday-morning disease, tying up, set fast, azoturia, chronic intermittent rhabdomyolysis, post-anesthetic myopathy, and equine rhabdomyolysis syndrome. A great deal of controversy has arisen regarding the cause of this syndrome. ER has been recognized for years, but the cause or causes had remained elusive. It is important to bear in mind that ER is a clinical sign, not a disease diagnosis. History indicates that studies of ER have reported a multitude of findings, and not all have stood the test of time, making interpretation of their studies difficult. Some conclusions proved to be secondary effects and some appear to have been wrong (i.e. lactic acidosis). Recent studies have detected specific causes of myopathy in specific breeds (2, 3, 4, 5). It is now clear that ER incorporates a number of different disease processes that share a common pathway of muscle pain.

The manifestation of ER in the horse is influenced by factors such as exercise routines, sex, age, and temperament of the horse as well as diet and presence of lameness (6). Horses with ER usually show signs of muscle stiffness, shifting hind limb lameness, elevated respiratory rate, sweating, firm painful hindquarter muscles, and reluctance to move that last for several hours. A diagnosis of ER is based on clinical signs of muscle stiffness and pain after exercise in conjunction with elevation in serum creatine kinase (CK) and aspartate transaminase (AST) activity. The degree of elevation of these enzymes in serum is dependent on the severity of muscle damage as well as the length of time that has elapsed between the sample collection and the occurrence of muscle damage (7). Approximately 3% of exercising horses are reported to have had an episode of ER in the last 12 mo (5), with higher rates reported among racehorses, as high as 13%. It has also been shown to occur just as frequently in polo horses (8) and competition event horses (McGowan, unpublished). With severe ER, electrolyte abnormalities such as hyponatremia (low sodium), hypochloremia (low chloride), hypocalcemia (low calcium), hyperkalemia (high potassium), and hyperphosphatemia (high phosphate) may occur (9). These derangements result from sweating as well as shifting of fluid and electrolytes down a concentration gradient into damaged muscle.

It is now believed that many cases of ER are attributed to one of two underlying causes, both thought to have a genetic bases: 1) equine polysaccharide storage myopathy (EPSSM) in Quarter Horses, Warmbloods, Draft breeds and their crosses (2, 10, 11, 12) *See EPSSM – Keeping up with Evolution, for more detailed information,* or 2) a defect in intracellular skeletal muscle calcium regulation (similar to malignant hyperthermia) in Thoroughbred and Standardbred racehorses (3).

While EPSSM is usually manifest as ER (10), it has been reported to be associated with post anesthetic myopathy, generalized weakness (13) and with gait abnormalities of the hind limbs including shivering (14). As time passed and veterinary care evolved, another manifestation was recognized in the high incidence of post-anesthetic myopathy, particularly in Draft and Quarter Horse breeds. In fact, the sensitivity of Draft horses to general anesthesia made veterinary surgeons reluctant to put Drafts "under". It was proposed that the heavy muscling and large body mass of both breeds, but specifically Drafts, made them more prone to ischemic damage and/or muscle necrosis while lying on the surgery table anesthetized. But decreased blood pressure during anesthesia has been shown to cause post-anesthetic myopathy in any horse (15), regardless of their body mass. Given this, it is somewhat surprising that with marked improvement in padding of surgical tables, positive pressure ventilation and continuous monitoring of blood pressure, post-anesthetic myopathy still occured. Recent research has now shown that these two entities are inter-related.

While the exact pathogenesis is not fully known, EPSSM is associated with abnormal glucose uptake into muscle of affected horses (16). It is characterized on muscle biopsy by accumulations of glycogen and amylase resistant complex polysaccharide within the type-2 myofibers (2, 17); myofiber size variations, hypertrophy, internal nuclei and interstitial fat accumulation may also be observed (13, 17). Based on the characteristic finding of glycogen-related polysaccharides in muscle from affected horses and lots of research, the logical conclusion was that there must be something wrong with carbohydrate metabolism in these horses. The focus moved to whole body glucose metabolism and the uptake of blood glucose into muscle cells following a high starch and sugar meal in these horses. Groups working on this problem independently began testing the effects of a diet with reduced starches and sugars and added fat as an alternative energy source. It very quickly becomes clear that this sort of diet is exactly what these horses needed.

Very recently, breeding trial of Quarter Horses with EPSSM were conducted that suggested the mode of inheritance as an autosomal dominant trait. Three independent publications looking at genome information, DNA fragment assays and the genetics of EPSSM families of horses identified the *GYS1* mutation. This dominant mutation accounts for ~80% of EPSSM cases in Quarter Horses and related breeds, and is now termed **type-1 EPSSM** . The 20% of EPSSM horses that do not possess the GYS1 mutation most likely have a distinct glycogen storage disease (4, 5), now termed **type-2 EPSSM**. In a subset of type-1 EPSSM horses, the clinical severity is modified by a second genetic mutation for **malignant hyperthermia (MH)** (McCue, unpublished). Horses with both the GYS1 and MH mutation have more severe clinical signs and poorer responses to management strategies. Although the MH mutation is present only in Quarter Horses and Quarter horse-related breeds, the type-1 EPSSM mutation has been found in at least 17 different horse breeds (5), and it is likely to have originated before the formation of the modern breeds known today (4). Type-2 EPSSM also seems to be found in Warmblood and light breeds other than Quarter Horses. The genetic test for type-1 EPSSM and the modifying gene MH are now commercially available at the University of Minnesota Diagnostic Laboratory. Diagnosis of type-2 EPSSM will require examination of a muscle biopsy until the genetic basis for this disorder is fully identified.

The cause of ER in Thoroughbreds, Standardbreds, and other non-Quarter Horse light horse breeds (when not EPSSM) is still controversial, but ongoing studies by one group is pursing the possibility of abnormal calcium handling in affected Thoroughbreds (18). Calcium handing defects can be specific and associated with defects of the ryanodine receptor, the primary calcium-releasing channel of skeletal muscle, in which case the result can be malignant hyperthermia in people. Malignant hyperthermia testing has long relied on *in vitro* caffeine and halothane contracture testing performed on people and horses with ER (3). But, abnormal contracture testing and predisposition to malignant hyperthermia in man can also be a non-specific response associated with a variety of myopathic and neurogenic disorders (19). A similar situation may exist in horses. A muscle biopsy can be performed to help with this determination. Curiously, though, Thoroughbreds with recurrent ER have been shown to respond to the same type of high fat and low starch and sugar diet designed for Quarter Horse, Draft and Warmblood horses with EPSSM. The challenge in altering the diet of Thoroughbred and Standardbred racehorses with recurrent ER is in supplying an adequate number of calories in a highly palatable feed to meet their daily energy demands. This can be very difficult to achieve by blending individual components, but achievable by feeding pelleted, specialized commercial diets. These feeds typically should contain < 20% starch (or non structural carbohydrates, NSCs) by weight and > 10% fat by weight with a high-fiber component.

Owners need to be aware that any horse diagnosed with ER will always have an underlying predilection for muscle soreness. The best that can be done is to manage horses in the most appropriate fashion to minimize clinical signs. Ample free exercise is always recommended. Moving around, even in a dry lot, is preferred to strict stall confinement, and seems to be beneficial in the long term. Recognize that the duration of exercise is as important as the intensity, and be sure to gradually introduce a work-out program. Be consistent with the program, minimizing the number of days without some form of exercise (20). Sporatic cases of ER may develop as a result of exercise beyond training adaption, injury from repetitive motion, heat exhaustion, or certain dietary imbalances. If a horse has experienced an episode of ER recently, two weeks of turnout and diet change are often beneficial before recommencing exercise. Exercise should then begin very relaxed and the horse should be allowed a long, low frame without collection at first. Successive daily addition of 2-minute intervals of walk and trot, beginning with only 5 minutes of exercise and working up to 30 minutes after 3 weeks, is often recommended. Owners often do not recognized that walking the horse for 10 minutes or more initially can trigger muscle soreness in EPSSM horses, so keeping horses with EPSSM fit seems to be the best prevention against further episodes of ER. This gradual approach to re-introducing exercise aims to enhance the oxidative capacity of skeletal muscle without causing cellular damage. The oxidative capacity of locomotor muscles in most Quarter Horse and Draft breeds is very low, but can be increased with daily exercise (21). Enhanced oxidative metabolism facilitates the metabolism of fat as an energy substrate.

The dietary modifications for EPSSM horses is designed to reduce the glucose load and provide fat as an alternate energy source. Anecdotally, owners report that this type of diet improves clinical signs of ER (20, 22). The beneficial effect of the low-starch, high-fat diet results in less glucose uptake into muscle cells and provides more plasma free-fatty acids in muscle fibers for use during aerobic exrcise (21). Studies show that these changes alone are not beneficial, and must be instituted with an exercise program to show clinical improvement (20, 22). With adherence to both diet and exercise recommendations, 80% of horses show notable improvement in clinical signs and many return to an acceptable level of performance.

It is an exciting time for research into equine muscle disease. Determining the underlying cause or causes will not be easy.

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