



All breeds of horses can be impacted by tying up or what is commonly referred to as exertional rhabdomyolysis in the scientific community

Understanding Muscle Cramps

MULTIPLE FACTORS CAN CAUSE EXERTIONAL RHABDOMYOLYSIS

By AMANDA DUCKWORTH

TYING UP IS not uncommon in horses, but it is extremely uncomfortable and potentially very dangerous. It goes by many names and is somewhat like excessive cramps in humans. It has been associated with electrolyte imbalances but also can be correlated to genetics, exercise, and diet.

Although many know the name tying up, it is scientifically referred to as exertional rhabdomyolysis (ER) and is also sometimes called azoturia or Monday Morning Sickness.

Horses with ER can suffer from sporadic rhabdomyolysis or chronic rhabdomyolysis, the latter of which is often separated into recurrent exertional rhabdomyolysis (RER) or polysaccharide storage myopathy (PSSM). Depending on the cause of the muscle damage, it can also be non-exercise associated rhabdomyolysis or traumatic rhabdomyolysis.

In this realm, there is also myofibrillar myopathy (MFM), which is a genetic condition featuring abnormal build up of desmin in muscle tissues that can often

be confused with PSSM. Although it has been found in Thoroughbreds and Quarter Horses, it is a rarity in those breeds.

For an extensive overview of these disorders, the Merck Veterinary Manual provides “Exertional Myopathies in Horses” by Dr. Stephanie J. Valberg, which explains in detail the various conditions and which breeds are more susceptible to which forms.

“Exertional myopathy in horses is a syndrome of muscle fatigue, pain, or cramping associated with exercise,” explained Valberg. “Less common exertional myopathies that cause exercise intolerance without muscle necrosis include mitochondrial myopathies, type 2 polysaccharide storage myopathy, and myofibrillar myopathy in Warmblood and Arabian horses.

“Most commonly, exertional myopathies produce necrosis of striated skeletal muscle and are termed exertional rhabdomyolysis. Although exertional rhabdomyolysis was previously considered a single disease described as azoturia, tying-up, or cording up, it is now known to comprise several myopathies, which, despite similarities in clinical presentation, differ notably in etiopathogenesis.”

In general, ER can affect all breeds and relates to the breakdown of skeletal muscle fibers after exercise. It can lead to muscle spasms, stiffness, excessive sweating, and dark urine. If this sounds familiar, it may be because rhabdomyolysis is not limited to horses. Colloquially called “rhabdo,” it can affect multiple other species, including humans, as well. It is a serious medical condition involving the rapid breakdown of damaged skeletal muscle that can be life-threatening to horses and humans alike.

Tying up is a serious condition, and if a horse is exhibiting signs of it, it is important to contact a veterinarian. If it is exercise induced, that activity should stop immediately. Although different cases require different treatment

plans, some accepted general treatment options include: hydration, pain management, electrolytes, muscle relaxation, and blood and urine monitoring.

In March 2025, the Equine Veterinary Journal published “Characterization of phenotypic patterns in equine exercise-associated myopathies.”

“Given that horses are commonly used for athletic pursuits, it is perhaps unsurprising that exercise-associated muscle disorders are commonly recognized in this species,” explained researchers. “Often, affected horses are presumptively diagnosed with exertional rhabdomyolysis (ER), a clinically heterogeneous myopathic syndrome characterized by exercise-induced episodes of myofiber damage. Clinical signs of ER can include stiffness,



Large muscle groups are impacted during an episode of ER and giving a horse a proper cooling down after strenuous exercise is part of the remedy

muscle fasciculation, cramping, sweating, reluctance to move, myoglobinuria, and in severe cases recumbency, or death. Typically, the clinical presentations and severities of ER vary between both individuals and between episodes.”

Researchers designed a historical cross-section study, with a subsequent masked case-control validation study, to characterize phenotypic patterns across exercise-associated myopathies in horses.

An advertisement for Equiade Body Builder. On the left, a dark brown horse is shown in profile, running powerfully through a cloud of dust. In the center is a white plastic bottle of the supplement. The bottle has a black label with a white horse head logo and the text "EQUIADE SINCE 1984", "BODY BUILDER™", "CONTAINS GAMMA ORYZANOL", "Muscular Function & Support", and "Horse Supplement 60 Day Supply 32 FL. Oz. (960mL)". To the right of the bottle, the text "BUILD MUSCLE & STRENGTH" is in white, followed by "BODY BUILDER™" in large purple letters. Below this, it says "BOOST MUSCLE DEVELOPMENT & PERFORMANCE" in white. A list of three benefits follows, each preceded by a checkmark: "Contains Gamma Oryzanol", "Supports Stamina & Muscle Growth", and "Enhances Endurance & Power". At the bottom right, it says "TRUSTED SINCE 1984" in yellow. The bottom of the ad features a dark purple banner with the website "www.Equiade.com" in white on the left, and contact information on the right: an envelope icon followed by "info@equiade.com" and a telephone icon followed by "1-800-413-3702".

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According to researchers, the historical clinical and histological features from 109 muscle samples were used for k-means clustering and validated using principal components analysis and hierarchical clustering. Following that, 69 horses were used for a blinded histological study comparing two phenotypic groups with selected controls and horses with histopathological features characterized by myofibrillar disruption.

“Using clinical history and histopathological features from biobanked samples, we have identified a distinct exercise-associated myopathy phenotypic subtype we have termed EAMS, consisting of horses with weakness, perceived ataxia, muscle pain, gait abnormalities and reluctance to go forward under saddle,” concluded researchers. “This was validated using different horse groupings, variable groupings, and clustering methods, with similar clinical signs consistently identified. This EAMS subtype is distinct from the disorder referred to as equine MFM; indeed, MFM was not detected in these European horses. Further, there were no histopathological features that dis-



OUR INTEGRATIVE TRANSCRIPTIONAL AND BIOCHEMICAL METHODOLOGIES PROVIDE NOVEL INFORMATION ON GENE AND PROTEIN EXPRESSION IN MUSCLE OF STANDARD BREED RACEHORSE SUSCEPTIBLE TO RECURRENT BOUTS OF EXERTIONAL RHABDOMYOLYSIS.”

— BASEL

tinguished between classic RER and non-classic EAMS across breeds, indicating that this novel subtype has a similar non-specific myopathic appearance using a standard muscle staining panel.

“While it remains unclear whether this novel subtype represents a single

disease entity, and whether the practitioner-described clinical signs represent true associations, co-variables or simply, improper classifications, its recognition for both future genetic and clinical studies might improve study power and help end the long delay in research progress with exertional myopathic syndromes of horses.”

In terms of RER, it is estimated that about 5% to 10% of Thoroughbreds worldwide are affected. There is no singular diagnostic test for RER, but rather the diagnosis is determined via observation and patient history. It has been associated with an inability to properly regulate calcium levels inside muscle cells and there may be a genetic predisposition component involved.

In February 2021, PLOS One published “Pathways of calcium regulation, electron transport, and mitochondrial protein translation are molecular signatures of susceptibility to recurrent exertional rhabdomyolysis in Thoroughbred racehorses.”

“Recurrent exertional rhabdomyolysis (RER) develops in 5–10% of Thoroughbred racehorses, with intermittent



LEFT: COADY MEDIA; RIGHT: ANNE M. EBERHARDT

Keeping horses hydrated has myriad benefits. (Right) Blood tests and urinalysis are diagnostic tools in identifying ER

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episodes frequent enough in one third of RER susceptible horses to disrupt a regular training and racing schedule,” explained researchers. “Both environmental factors and a genetic predisposition impact the expression of RER with young, nervous, female horses in race training on high starch diets affected at highest frequencies.

“Although heritability of RER is estimated at 0.40, linkage analyses and genome-wide association studies so far have been ineffective at identifying a consensus chromosomal locus or gene associated with RER in Thoroughbred horses. This could be due to a polygenic mode of inheritance or post-translational modifications that arise in a stressful training environment.”

As researchers explained, a potential role of intramuscular calcium (Ca^{2+}) dysregulation in RER has led to the use of dantrolene to prevent episodes of rhabdomyolysis. For this study, they examined differentially expressed proteins (DEP) and gene transcripts (DEG) in gluteal muscle of Thoroughbred race-trained mares after exercise.

Mares in the study were divided into three groups of five. The first group of horses were susceptible to, but not currently experiencing, rhabdomyolysis. The second group was the control and made up of healthy horses with no history of RER. The third group consisted of RER-susceptible horses treated with dantrolene pre-exercise (RER-D). They were all stabled at the same training center in Lexington.

“RER-susceptible horses treated with dantrolene, which slows sarcoplasmic reticulum Ca^{2+} release, showed no DEG compared to control horses,” said researchers. “We conclude that RER-susceptibility is associated with alterations in proteins, genes and pathways impacting myoplasmic Ca^{2+} regulation, the mitochondrion and protein degradation with opposing effects on mitochondrial transcriptional/translational responses and mitochondrial protein content.



Quarter Horses are more prone to a certain type of ER than other breeds



Environmental factors play a significant role in tying up, particularly the stress of racing

“RER could potentially arise from excessive sarcoplasmic reticulum Ca^{2+} release and subsequent mitochondrial buffering of excessive myoplasmic Ca^{2+} .”

Thoroughbreds are far from the only breed affected by RER. Horses used for other types of racing, polo, eventing, and

endurance riding all face the challenges it can present. In October 2022, Genes (Basel) published “Enriched Pathways of Calcium Regulation, Cellular/Oxidative Stress, Inflammation, and Cell Proliferation Characterize Gluteal Muscle of Standardbred Horses between Episodes of Recurrent Exertional

Rhabdomyolysis.”

“In Standardbred horses with RER, muscle histology, biochemistry, exercise responses, electron transport chain coupling, and microarray analysis of gene expression have been investigated during an episode of acute rhabdomyolysis,” explained researchers. “These studies show that episodes of rhabdomyolysis occur intermittently, characterized by sudden increases in serum creatine kinase activity (CK) without accompanying lactic acidosis. Differential expression of Ca²⁺ regulatory, mitochondrial and metabolic genes, and altered mitochondrial coupling have been identified during acute rhabdomyolysis in Standardbred horses.

“Both an abnormality in intramus-

cular calcium regulation and disturbed mitochondrial function have been proposed as a cause of RER in this breed. Between episodes of rhabdomyolysis, Standardbred horses are as successful, or more successful racehorses, than horses with no history of RER and it is unknown if altered gene or protein expression persists in the muscle of Standardbred horses at this time point.”

For this study, researchers compared gluteal muscle histopathology and gene/protein expression in Standardbreds. Group one had nine horses in it, all with a history of, but not currently experiencing, rhabdomyolysis. Group two had seven horses, which served as the race-trained control.

“Our integrative transcriptional and biochemical methodologies provide

novel information on gene and protein expression in muscle of Standardbred racehorse susceptible to recurrent bouts of exertional rhabdomyolysis,” concluded researchers. “Gluteal samples were taken between episodes of rhabdomyolysis to define underlying characteristics of this disease. The integrated analysis revealed persistent alterations in expression of genes and proteins involved in calcium ion regulation, cellular/oxidative stress, inflammation, and regeneration as characteristic of gluteal muscle from RER-susceptible Standardbreds between episodes of rhabdomyolysis.

“Notably, differential gene expression of calcium ion regulation, oxidative metabolism, and cellular/oxidative stress are also



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characteristics of acute rhabdomyolysis in trotting racehorses which appear to persist for weeks between episodes could therefore potentially serve as therapeutic targets to mitigate rhabdomyolysis and its long-term effects.”

Unlike RER, polysaccharide storage myopathy (PSSM) is caused by abnormal accumulation of glycogen, which is a form of glucose or sugar. Like RER, PSSM can cause a horse to tie up and

“Equine polysaccharide storage myopathy (PSSM) is a specific form of exertional rhabdomyolysis in Quarter Horses (QH) and related breeds,” explained researchers. “The hallmark feature that led to the discovery of PSSM was aggregates of amylase-resistant polysaccharide (Ar-PS) in periodic acid–Schiff (PAS) stains of skeletal muscle.

“Both type 1 (PSSM1) and type 2

Diagnostic Laboratory database to find horses suitable for the study, and they used submissions between December 1993 and November 2021. In total, 64 PSSM2-QH, 30 PSSM1-QH and 185 control-QH were identified from a biopsy repository and clinical data. Their histopathology scores (0-3), glycogen concentrations and selected glycolytic enzyme activities were compared.

“Exertional rhabdomyolysis in PSSM2-QH occurred predominantly in barrel racing and working cow/roping performance types and improved with regular exercise and a low starch/fat-supplemented diet,” researchers concluded. “Histopathological scores, including the amount of amylase-resistant polysaccharide and glycogen concentrations were intermediate in PSSM2-QH with significant differences among groups.

“In PSSM2-QH, abnormal polysaccharide had a less filamentous ultrastructure than PSSM1-QH and phosphorylase and phosphofructokinase activities were normal. Seventeen of 30 PSSM2-QH with available pedigrees descended from one of three stallions within four generations. Of the 29 predicted high or moderate impact genetic variants identified in candidate genes, none were present in only PSSM2-QH and absent in control-QH. PSSM2-QH is a novel glycogen storage disorder that is not the result of a mutation in genes currently known to cause muscle glycogenoses in other species.”

While there is still a great deal to learn about different forms of tying up, there are some established diagnostic tools. They include blood work, urinalysis, muscle biopsy, and genetic testing. Both stress and diet can make a horse susceptible, so striving for comfortable living spaces and a nutritionally-balanced diet low in starch and sugar are also strategies to keep in mind. **BH**



Standardbreds are susceptible to multiple bouts of ER

experience muscle stiffness and pain after exercise. There are two known types of PSSM. Type 1 is caused by a genetic mutation, and there is a DNA test available. The exact cause of Type 2 is unknown but may be genetic.

Quarter Horses, along with Paints, Appaloosas, and draft breeds, are much more susceptible than Thoroughbreds to PSSM1. Thoroughbreds are extremely unlikely to have Type 1 PSSM but can suffer from Type 2 PSSM.

In July 2023, the Equine Veterinary Journal published “Type 2 polysaccharide storage myopathy in Quarter Horses is a novel glycogen storage disease causing exertional rhabdomyolysis.”

polysaccharide storage myopathy (PSSM2) are characterized by aggregates of abnormal polysaccharide in skeletal muscle. Whereas the genetic basis for PSSM1 is known (R309H GYS1), the cause of PSSM2 in Quarter Horses (PSSM2-QH) is unknown and glycogen concentrations not defined.”

For the retrospective case control study, researchers aimed to characterize the histopathological and biochemical features of PSSM2-QH and determine if an associated monogenic variant exists in genes known to cause glycogenosis.

Researchers accessed the Michigan State University Neuromuscular