CPD article

Exertional rhabdomyolysis: recent advances in knowledge

Our understanding of exertional rhabdomyolysis in the horse has advanced considerably over the past 10 years. Not long ago, this syndrome was considered to be a single disease entity, also known as azoturia or Monday morning disease. Now, several distinct and very different conditions that result in this common clinical presentation have been recognised. The most documented of these conditions are recurrent exertional rhabdomyolysis (RER) and polysaccharide storage myopathy (PSSM), the latter having been recently classified into type 1 and type 2 PSSM. The availability of genetic testing and widespread use of muscle biopsy sampling have facilitated clinical diagnosis of underlying myopathies in the field.

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While some areas of equine internal medicine have advanced relatively slowly over the past decade, understanding of equine muscle disorders has progressed considerably. This rapid expansion of knowledge has partly been precipitated by the sequencing of the horse genome — which was completed in 2007 and has paved the way for the identification of specific genetic defects that predispose a horse to exertional rhabdomyolysis — as well as by the evaluation of muscle biopsy samples from horses with muscle disease. This article covers the changes in understanding of the aetiology of exertional rhabdomyolysis that have evolved over the past decade.

Exertional rhabdomyolysis (also known as azoturia or Monday morning disease) was previously considered to be a single disease entity. However, it is now appreciated that there are several very different conditions that affect skeletal muscle function in different ways. Any one of these disorders may result in a common clinical presentation that includes stiffness, reluctance to move, muscle fasciculations, myoglobinuria and sweating following exercise. These clinical signs usually occur in association with increases in plasma muscle enzyme activities.

Causes of exertional rhabdomyolysis

Some horses may experience isolated bouts of tying-up purely because of overexertion. Many horses that experience recurrent bouts of rhabdomyolysis have a proven or likely genetic basis to their presentation. Two genetic conditions have been identified to date: recurrent exertional rhabdomyolysis (RER); and polysaccharide storage myopathy (PSSM).

Recurrent exertional rhabdomyolysis

RER affects Thoroughbred and Thoroughbred crosses, and possibly other breeds such as Standardbreds. RER is thought to be associated with the abnormal release of calcium within muscle cells, resulting in abnormal muscle contracture (Lentz et al, 1999).

The pattern of inheritance in several breeding lines suggests that RER is a genetic condition (Dranchak et al, 2005). Recent genome-wide association studies have identified several areas of a horse's genome, in particular on chromosome 16, that are highly associated with the disease (Fritz et al, 2012). Work continues to evaluate specific genes located in this area and hone in on one or several causative mutations.

As changes on histopathology of muscle biopsy samples in cases of RER are non specific, and a specific genetic mutation has not been identified, RER is diagnosed on the basis of clinical history, elevated muscle enzyme activity and evidence of previous muscle damage on histopathology in a Thoroughbred or related horse.

PSSM (types 1 and 2)

PSSM was first described in the early 1990s in a subset of Quarter Horse and Appaloosa related breeds with clinical signs of rhabdomyolysis (Valberg, 1992). The disease has been identified in a variety of breeds across Europe and North America (McCue, 2008a; Stanley et al, 2009) (*Table 1*), with a high prevalence in Continental draught breeds.

The clinical presentation of PSSM varies from vague signs of poor performance or back pain to rhabdomyolysis. The disease is associated with the accumulation of increased glycogen and abnormal polysaccharide inclusions in muscle fibres. This is associated with a reduction in cellular energy availability (Annandale et al, 2005). PSSM is associated with increased insulin sensitivity in some breeds (Annandale et al, 2004), but not others (Firshman et al, 2008).

In 2008, a dominant mutation in the glycogen synthase 1 (GYS1) gene was identified as the cause of PSSM (McCue, 2008b) in approximately two thirds of horses with the condition. This led to the disease being classified into PSSM1 for horses with the GYS1 mutation and PSSM2 for horses with abnormal polysaccharide in their skeletal muscle that lack this gene mutation. A genetic test is now available for PSSM1, which can be performed on DNA extracted from blood collected into EDTA or hair roots; PSSM2 can be diagnosed only from a muscle biopsy.

Recent work suggests that the abnormal accumulation of polysaccharide in Arabian endurance horses with PSSM2 results from disruption in myofibrillar proteins rather than a primary glycogen storage disease (Valberg et al, 2015).

Other causes of rhabdomyolysis

Several earlier studies have suggested acquired causes of rhabdomyolysis (Freestone et al, 1991; Harris, 1991; Beech et al, 1993), such as sex hormones and electrolyte imbalances. Most of these suggested risk factors are yet to be corroborated, with different studies yielding conflicting results; it remains possible that these risk factors may increase the risk of clinical disease in a genetically susceptible animal.

An increase in muscle biopsy sample submission, alongside the establishment of laboratories that deal only with muscle biopsy samples, has led to some less common conditions being identified. In humans, several mitochondrial defects lead to rhabdomyolysis with profound exercise intolerance and there are reports of similar pathology in the horse (Valberg et al, 1994; Van Driessche et al, 2015). An unusual case of a vacuolar myopathy — a condition seen in people but not previously described in the horse — was recently identified in a Warmblood mare with intermittent mild rhabdomyolysis (Massey et al, 2013). In humans, there are many more causes of rhabdomyolysis that, as yet, have not been described in equine athletes. It is expected that more conditions will be discovered as muscle pathology is more extensively evaluated.

Muscle enzyme activity

Muscle enzymes creatine kinase (CK) and aspartate aminotransferase (AST) are released from muscle cells following damage. CK levels increase most rapidly while AST peaks approximately 24–48 hours after muscle damage. While CK is considered to be specific for muscle damage, AST is also released from sources such as the liver, so muscle enzymes should be interpreted in conjunction with other liver parameters to rule out hepatic causes of increased enzyme activity. Sampling 4–6 hours after 15 minutes of submaximal exercise (trot and canter work) can increase the sensitivity of muscle enzyme assessment in the detection of subclinical myopathy.

Table 1. Breeds in which the causative GYS1 mutation for type 1 polysaccharide storage myopathy has been identified to date

Quarter Horse
Paint
Appaloosa
Warmblood
Haflinger
Morgan
Mustang
Rocky Mountain horse
Belgian draught
Percheron
Shire
Suffolk Punch
Hanoverian
Rheinlanger
Cob Normand
Connemara x Welsh pony
Connemara x Thoroughbred
Cob
Argentinian polo pony
Arab x
Thoroughbred x
Polo pony
South German Coldblood
Saxon-Thuringian Coldblood
Exmoor pony
Continental European draught breeds e.g. Ardenner, Belgian trekpaard

As the understanding of muscle diseases has evolved, it has become apparent that the different muscle diseases invoke different responses in muscle enzyme activity following exercise. In particular, several studies have described only small increases in post-exercise muscle enzyme activity in horses with PSSM1 (Schwarz et al, 2011; Naylor et al, 2012) although in both studies these research animals were apparently asymptomatic.

Muscle biopsy

Collecting a muscle biopsy is a simple procedure that can be easily performed in a sedated horse. The technique can provide useful information regarding the aetiology of exertional rhabdomyolysis, and can therefore guide therapy and provide useful prognostic information. Biopsies are usually collected from the semimembranosus or gluteal muscles, as these are rich in type 2 muscle fibres. Type 2 muscle fibres are most commonly affected in most diseases that cause exertional rhabdomyolysis such as PSSM.

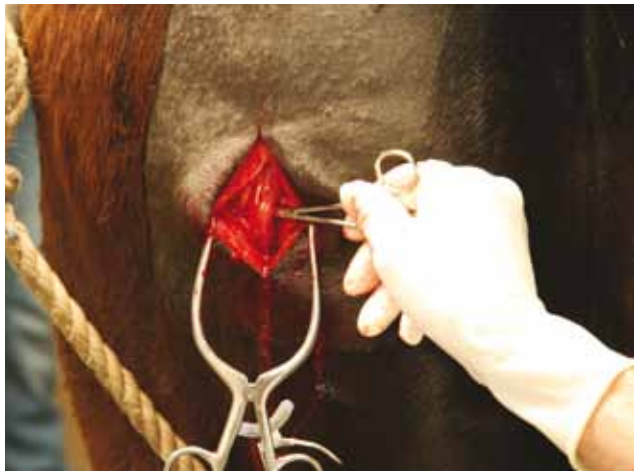

Figure 1. Collecting a muscle biopsy.

The area overlying the muscle is clipped and prepared aseptically, after which 2–5 ml of local anaesthetic is infiltrated subcutaneously. The skin and subcutaneous tissues are incised and retractors can be useful at this stage to visualise the underlying muscle. Two parallel vertical incisions, approximately 2 cm in length and 1 cm apart, are then made into the muscle. Haemostats can then be used to undermine the muscle tissue before incising along the proximal and distal margins (Ledwith and McGowan, 2004). The muscle defect and overlying subcutaneous tissue and skin are then closed (*Figure 1*).

Usually, a 2 cm by 1 cm sample is collected. This is divided into two, with one half being placed into an empty sterile pot and transferred to the diagnostic laboratory on ice packs, while the second piece is placed in formalin in case of delays in transportation. It is advisable to liaise with the laboratory before sample submission and send the same via courier for arrival on the same or the next day (*Table 2*).

Managing muscle disease in the horse

Several studies have shown dietary modification and regular exercise have a beneficial effect in managing horses that experience recurrent bouts of exertional rhabdomyolysis, particularly those with PSSM. These modifications often benefit Thoroughbreds with RER as well.

Horses should continue to receive 1.5–2% of their bodyweight as roughage, ideally with a non-structural carbohydrate content of less than 10% (Borgia et al, 2011). In some cases, no caloric supplementation is required; where energy requirements are greater, feeding a diet low in starch and high (>13%) in fat has been shown to reduce muscle enzyme responses to exercise in horses with PSSM1 (Ribeiro et al, 2004).

Manufactured diets are available that meet these requirements; alternatively, vegetable oil may be added to the feed, up to a maximum of 1 ml/kg bodyweight. Vitamin E should be supplemented (5000 IU α-tocophorol/500kg bodyweight) in a horse on a high fat diet to offset increased free radical production. Dietary changes should be made slowly.

To date, there are no dietary studies of horses with PSSM2, although it is assumed that management recommendations for PSSM1 will also benefit these cases.

Regular (daily) exercise along with pasture turnout are beneficial and the prognosis is more favourable when both exercise and dietary recommendations are followed (Firshman et al, 2003). The amount of exercise will depend on the fitness and discipline of the horse; crucially, rest days should be avoided.

Adaptation to these changes should be expected to take several months although a clinical improvement may be seen within several weeks.

Electrolyte supplementation is often advocated; however, note that the wide daily variation in the fractional excretion of electrolytes in the horse render it of little value as a diagnostic test for specific electrolyte derangements in most cases.

While vitamin E may be administered to protect against exercise-induced free radical muscle damage, a deficiency in horses with exertional rhabdomyolysis has not been demonstrated. Vitamin E supplementation may be beneficial where a dietary deficiency is suspected.

Dantrolene sodium has been used prophylactically in Thoroughbred racehorses to reduce calcium release within muscle. Dantrolene was found to reduce muscle enzyme activity and the incidence of rhabdomyolysis when administered 800 mg orally to a cohort of 77 racehorses in training (Edwards et al, 2003), and also in five horses with a history of RER when administered orally at a dose of 4 mg/kg 90 minutes before exercise (McKenzie et al, 2004).

Conclusions

Exertional rhabdomyolysis is a syndrome that affects a variety of horse breeds and there are a number of aetiologies.

Muscle biopsy and genetic testing are the keys to establish-

Table 2. Summary of key pathological findings observed in muscle biopsy samples from horses with exertional rhabdomyolysis

Pathological features	Significance
Internalised nuclei	Muscle fibres that have undergone regeneration following injury
Increased fibre size variation	A feature of muscle regeneration
Increased glycogen	Often found in polysaccharide storage myopathy (PSSM)
Diastase-resistant polysaccharide	Characteristic for PSSM
Subsarcolemmal vacuoles	Often found in PSSM
Fibrosis	Chronic, irreversible muscle damage

KEY POINTS

- Different conditions can cause horses to tie-up.
- Muscle enzyme activities are measured to screen for these conditions, but responses to exercise vary between diseases.
- Muscle biopsy sampling and genetic testing can help differentiate between specific conditions.
- Exercise and dietary modification are the mainstay of patient management.

ing a definitive diagnosis where an underlying myopathy is suspected. For example, in breeds with a high prevalence of PSSM1, such as Percheron or Quarter Horse related breeds, genotyping for the GYS1 mutation may be preferred. Conversely, the GYS1 mutation has yet to be identified in a Thoroughbred horse, so a muscle biopsy would be the diagnostic test of choice.

There is no test for diagnosing RER definitively as yet but, should a genetic mutation be identified, such a test would rapidly become available.

In cases that do not respond to symptomatic management, muscle biopsy should be performed to evaluate underlying muscle pathology and rule out more unusual disorders. LS

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