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Skeletal muscle displays a limited pathological response to disease. As such, it is not surprising that the phenotypes of exercise-related myopathies with apparently different underlying causes look similar. Thus rhabdomyolysis in the young Thoroughbred filly clinically resembles rhabdomyolysis in a child’s pony or a Warmblood cross used for hunting, even though the diseases may have very different aetiologies. Muscle contracture, stiffness and pain associated with (sometimes) marked elevations in the muscle-derived enzymes, CK and AST, are sufficient to confirm that muscle is involved.

A variety of acquired factors underlying the development of exertional rhabdomyolysis is proposed, supported by evidence from other species. Unfortunately, for some proposed causes, the evidence remains speculative or hard to document with certainty due to various diagnostic constraints. Current and historical acquired causes that are proposed include overexertion or exhaustion, oxidative injury, eccentric contraction, hormonal influences and electrolyte abnormalities. The evidence for and against these suggested causes will be discussed.

We currently recognise 2 common forms of exercise-related myopathy in horses underising genetic causes. These include a condition examined extensively in a group of Thoroughbreds in the USA that has been termed ‘recurrent exertional rhabdomyolysis’ (RER) (Lentz et al. 1999) and ‘polysaccharide storage myopathy’ (PSSM or EPSM) (McCue et al. 2008; Stanley et al. 2009). These conditions have clinical and clinicopathological similarities and are managed similarly, though they also have key differences and breed susceptibilities (Valberg et al. 1999).

### Recurrent exertional rhabdomyolysis

Estimates of the prevalence of exercise-associated rhabdomyolysis in Thoroughbreds suggests that 5–7% of Thoroughbreds worldwide are affected (MacLeay et al. 1999a; McGowan et al. 2002; Cole et al. 2004), although it remains unknown whether all these animals have the same disorder. Pedigree analysis of some lines of Thoroughbreds in the USA supports autosomal dominant inheritance of the trait (MacLeay et al. 1999b; Dranchak et al. 2005). An abnormality in muscle calcium regulation identified in some Thoroughbreds shares certain experimental similarities to a condition recognised in humans and other species, known as malignant hyperthermia (MH). In particular, muscle from horses with RER and other species with MH is hypersensitive to agents (such as caffeine and halothane) that stimulate release of calcium from the muscle calcium store (sarcoplasmic reticulum) through a calcium release channel known as the ryanodine receptor (RYR1) (Lentz et al. 1999, 2002; Bendahan et al. 2004). However, although MH has been reported in some horses following halothane anaesthesia, and indeed, though an RYR1 receptor mutation has been identified in MH-susceptible Quarter Horses (Aleman et al. 2004), Thoroughbreds with abnormal calcium regulation do not share the same mutation and there is evidence suggesting that the RYR1 receptor is not involved in Thoroughbred RER (Dranchak et al. 2006). As yet, genetic studies have failed to identify a causative mutation(s) in affected Thoroughbreds.

The pathogenesis of recurrent exertional rhabdomyolysis also remains unknown, although raised sarcoplasmic calcium concentration may play a key role - for example increased intracellular calcium is known to be the forerunner of several myopathies in humans, often through activation of calpain-mediated apoptosis. Intriguingly, Standardbred horses with a disease similar, if not identical to RER in Thoroughbreds, perform better than matched controls, suggesting the possibility that selective breeding has inadvertently been responsible for maintenance of the trait in racehorses (Isgren et al. 2010). Consequently, the trait itself may confer performance advantages that intermittently result in an episode of rhabdomyolysis - perhaps as a result of the effects of modifying genes or the environment. It is known, for example, that horses susceptible to RER are more likely to be female and nervous animals (MacLeay et al. 1999a; McGowan et al. 2002; Isgren et al. 2010). The explanation for this epidemiological data remains unclear.

The aetiology and pathogenesis of RER remain elusive. It is likely that a combination of genetic techniques, combined with a better, more specific approach to phenotyping affected animals will help establish the genetic cause of RER in horses and in so doing, enable us to determine whether the disease is indeed a single entity, and whether the disease is caused by a monogenic or polygenic disorder. Improved understanding of the pathophysiology may lead to improved management and treatment strategies.

### References


Hall 1A ■ Thursday 8th September


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