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Aetiology and Pathophysiology of Exertional Rhabdomyolysis

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Introduction

Recent years have seen huge strides in the veterinary profession’s understanding of the cause and pathophysiology of equine myopathies, in particular, recognising that the syndrome of ‘tying up’ has several, and perhaps multiple causes. Skeletal muscle displays a somewhat 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. The similar clinical presentations help explain why it took a long time to recognise that there are several underlying causes of tying up.

ACQUIRED CAUSES

A variety of acquired factors underlying the development of exertional rhabdomyolysis (ER) are proposed, some of which are supported by evidence from other species. Although important as specific causes in normal horses, some apparently acquired causes may be associated with underlying genetic predisposition to ER. 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.

Overexertion

Extreme or unaccustomed exercise predisposes horses to rhabdomyolytic attacks. Muscle damage in such cases may include a combination of physical damage incurred during excessive eccentric contractions, metabolic exhaustion and oxidative injury.

Eccentric contraction

Delayed onset muscle soreness in humans is associated with damage caused by excessive eccentric contractions (contraction during muscle lengthening). Although the mechanism is poorly understood, there are prominent signs of damage within a muscle following eccentric contractions that include disruption of sarcomeres. This damage is reflected by (sometimes considerable) elevations in serum muscle enzyme activities and triggers a local inflammatory response accompanied by oedema. It is unknown whether horses experience this syndrome, however it seems likely.

Metabolic exhaustion

Exceeding the level of training in a horse either by excessive endurance exercise or overexertion when galloping is believed to be a common cause of acute ER in horses (Snow
and Valberg 1994). Although the causes are numerous and likely involve electrolyte imbalances and hyperthermia, in certain cases a presumed underlying factor is the deficiency of ATP, which results in an inability to maintain ion homeostasis.

**Antioxidant status**

Free radicals are widely believed to cause post exercise stiffness and fatigue in muscle, through several deleterious mechanisms that include the peroxidation of lipid membranes. Cell damage is normally minimised by the action of a complex cascade of free radical scavengers and antioxidants, including vitamin E and the selenium-dependent enzyme, glutathione peroxidase. When antioxidants fail to quench free radicals sufficiently, the body is subjected to so-called ‘oxidant stress’ (Ji and Leichtweis 1997). Evidence suggests that exercise-induced oxidative stress occurs in horses, but there is no clear association with muscle damage (Chiaradia et al. 1998). This is supported by studies demonstrating that antioxidant supplementation fails to attenuate exercise-induced elevations in plasma CK activity in horses, (Brady et al. 1978; Siciliano et al. 1997; White et al. 2001) There is therefore no good evidence that oxidant stress plays a primary role in ER. Despite this, during conditions likely to result in significant oxidant stress, such as very strenuous or prolonged exercise, antioxidant deficiencies may exacerbate muscle damage caused by other mechanisms.

**Electrolyte imbalance**

Published and anecdotal reports of improvement following correction of electrolyte clearance ratios, (Harris and Colles 1988) underlie the interest in this area. In a group of 38 ER-susceptible Thoroughbreds, about a third had potassium clearance ratios of less than 30% or low chloride clearance, (Beech et al. 1993) These differences could potentially reflect differences in the handling of electrolytes by ER-susceptible animals, but ER-prone horses exhibit the same dietary-induced alterations to electrolyte clearance ratios as normal animals (McKenzie et al. 2002). In comparison with controls, normal Thoroughbreds administered frusemide and sodium bicarbonate developed lower plasma calcium, chloride, magnesium and potassium concentrations. Following exercise, serum CK activity was found to be significantly higher in the treated group (Freestone et al. 1991). Some evidence therefore suggests that electrolyte imbalance may play a role in the development of certain forms of the disorder.

**Hormonal influence**

Many studies report a higher incidence of ER in female horses compared with males (Harris 1991; MacLeay et al. 1999a; McGowan et al. 2002). No correlation was found however between the stage of the oestrus cycle and plasma CK activities in thoroughbreds in training (Frauenfelder et al. 1986), suggesting that a direct association of female sex hormones with ER is unlikely. The higher incidence of ER in females remains unexplained, although it may relate to differences in temperament.

**Infectious causes**

Equine herpes virus 1 (EHV1) infection was proposed as causing an outbreak of ER in a training yard, where several horses seroconverted to the virus (Harris 1990). Equine Influenza Virus (EIV) has also been diagnosed by seroconversion as the potential cause of certain equine myopathies (Freestone and Carlson 1991). Both EIV and EHV1 infections are common in groups of young racehorses and cause and effect have not been fully established; as with other acquired causes, viral infection may modify the phenotype of genetically susceptible horses.

**INHERITED CAUSES**

We currently recognise several forms of exercise-related myopathy in horses with underlying genetic causes. These include a condition examined extensively in a small group of Thoroughbreds in the USA that has been termed ‘re-
current exertional rhabdomyolysis’ (RER) (Lentz et al. 1999) and another condition, termed ‘polysaccharide storage myopathy’ (PSSM or EPSM) (Valberg et al. 1992; Valenti et al. 2000). These conditions have clinical and clinicopathological similarities and are managed similarly, though they also have key differences and breed susceptibilities (Valberg et al. 1999) and aetiologies.

**Recurrent exertional rhabdomyolysis**
The word ‘recurrent’ in Thoroughbreds with exercise-related myopathy has been used variably to describe certain Thoroughbreds with documented abnormalities in muscle calcium regulation (Lentz et al. 1999), a wider group of Thoroughbreds with an apparent inherited form of ER (MacLeay et al. 1999b) and all Thoroughbreds with a susceptibility to the syndrome. In humans there are many genetic causes of rhabdomyolysis (e.g. mutations in genes encoding enzymes involved in cellular metabolism or structural proteins); it is currently unknown how many different forms of rhabdomyolysis affect Thoroughbreds.

Estimates of the prevalence of exercise-associated rhabdomyolysis in Thoroughbreds suggests that 5-7% of Thoroughbreds worldwide are affected (Cole et al. 2004; MacLeay et al. 1999a; McGowan et al. 2002), 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 (Dranchak et al. 2005; MacLeay et al. 1999b). Given that acquired forms of rhabdomyolysis are common in humans and other species it seems possible, or likely that some Thoroughbreds develop acquired forms of the syndrome as a result of some triggering environmental or management factor (MacLeay et al. 1999a).

Despite this, it is not possible to rule out a common underlying genetic predisposition within the breed: it is well known that external factors modify the phenotype in many genetic conditions. Furthermore, epidemiological evidence suggests that other breeds likely have the same disorder (Standardbreds in particular) (Isgren et al. 2010).

The 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) (Bendahan et al. 2004; Lentz et al. 1999; Lentz et al. 2002). However, though 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. 2004). Given that inhalational anaesthesia is common in equine veterinary work, but MH-like episodes are extremely rare, and certainly more scarce than ER, this seems unsurprising.

Despite this, the basic research similarities between RER and MH do still suggest the possibility of involvement of another protein or proteins that regulate intracellular calcium concentration in muscle. Indeed mutations in other proteins are known to cause or are implicated in human MH. The search for a gene or genes mutated in Thoroughbreds continues.

**Polysaccharide Storage Myopathy**
Polysaccharide storage myopathy (PSSM or EPSM) can be definitively diagnosed by muscle biopsy. Pathognomonic changes include diastase-resistant inclusions detected by Periodic Acid Schiff staining. Horses with this disorder are hypersensitive to insulin and clear glucose from the circulation more rapidly than normal animals (Annandale et al. 2004). This disease was first reported in detail in Quarter Horses with exertional rhabdomyolysis in the USA (Valberg et al. 1992). Since then, a disease with similar, if not iden-
tical histopathological features has been reported in a variety of other breeds, in particular draught horses ((McCue et al. 2006; Valentine et al. 1997; Valentine et al. 2001) in several countries, including the UK (McGowan et al. 2003). The Comparative Neuromuscular Diseases Laboratory at the Royal Veterinary College has since diagnosed this condition in a number of breeds, including ponies, cobs and Connemaras (Stanley et al. 2009). (Although there are sometimes clinical differences in the presentations of this disease (rhabdomyolysis in athletic animals and weakness or muscle atrophy in the draught horses) there is strong evidence that these diseases share the same underlying genetic cause (genotype). Early evidence suggested that this disorder in Quarter Horses was inherited as an autosomal recessive trait (Valberg et al. 1996), however more recent data suggests that in fact the disease is inherited as an autosomal dominant trait (McCue et al. 2007). A mutation in the glycogen synthase gene (GYS1) was reported, first in Quarter Horses discovered, in affected Quarter Horses, Belgian Draught horses and Warmbloods (McCue et al.2008) and has since been reported in many other breeds (Stanley et al. 2009). Furthermore, the finding that some horses with histopathology consistent with PSSM do not have the GYS1 mutation, reveals that other forms of PSSM exist. Currently these cases are classified as PSSM2 (Stanley et al. 2009).

CONCLUSIONS

There have been significant advances in clinical and basic research of equine neuromuscular diseases associated with tying up in recent years, advances that have important implications for veterinary surgeons. Whilst a better understanding of the pathophysiology of these conditions makes this a more rewarding time to be investigating and treating horses with these conditions, unanswered questions remain and numerous additional questions have arisen. More work is required in this important field.

FURTHER READING


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