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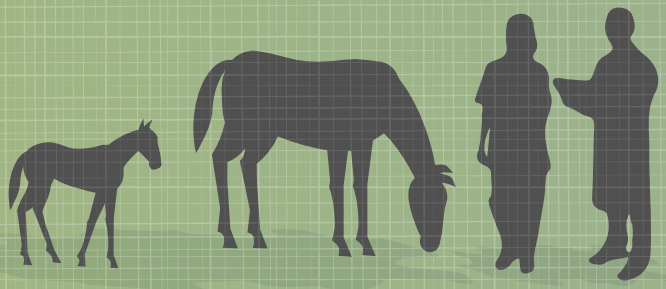

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Clinicopathological assessments and muscle biopsy in horses with neuromuscular disease

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Horses with underlying neuromuscular disease are usually recognised on the basis of their history (for example, stiffness post-exercise) and physical examination (muscle pain, swelling, atrophy or paresis), and the diagnostic suspicion can be strengthened by demonstration of elevated serum or plasma activities of muscle-derived enzymes, such as creatine kinase (CK) and aspartate amino transferase (AST). However, in investigating horses with poor performance, it is not uncommon to identify (apparently) subclinical elevations in CK and AST and determining the significance of such elevations is difficult. Furthermore, various myopathic disorders exist in which CK and AST activities are normal, but that present as poor performance or paresis. This presentation will cover approaches to these scenarios.

Muscle tissue has a variety of enzymes that perform normal functions, some (such as CK) being more specific for muscle damage than others (such as AST). CK will typically peak 6–12 hours following an insult, and then decline with a half-life of approximately 12 hours. In contrast, AST activity peaks about 24 hours following a muscle insult and can remain elevated for several days to weeks. Consequently, observation that CK remains elevated for several days (or is consistently mildly elevated in successive biochemistries taken on different occasions) likely reflects ongoing or repeated muscle-specific insults.

In horses with histories compatible with an exertional myopathy, plasma CK and AST activities are often normal by the time of veterinary examination. In these cases, a detailed history combined with an exercise test can be beneficial. Exercise testing is usually performed with the goal of eliciting a subclinical rise in CK (or AST) that can be detected biochemically. Unfortunately, there is no standardised protocol that has been widely followed in horses and so extrapolating amounts of exercise for different breeds, different diseases and horses with varying levels of fitness is difficult. Typically however, 20 minutes of light-moderate exercise (trot) on the lunge is used with pre-, 4 h and 24 h assessment of CK and AST activity. However, myopathic horses can vary considerably with their percentage rise in CK after exercise – some have no change at all, despite prominent muscle disease. As such, exercise tests remain a useful rule-in, but not a very useful rule-out (i.e., specific, but not sensitive).

Equine myopathies can usually be categorised (with some overlap) as exertional and nonexertional. Typically, exertional myopathies (rhabdomyolysis) are seen in athletic horses, during or shortly after exercise, in animals that are otherwise regarded as normal between episodes. While a variety of acquired conditions have been postulated, many horses likely have underlying genetic predisposition to this trait, and it may be that the proposed acquired causes are in fact environmental factors that can modify the phenotype in a genetically susceptible animal. Nonetheless, as in humans, overexertion likely is a significant cause of exertional myopathy in some horses.

Horses that have repeated myopathic exercise-associated episodes are more likely to have a genetic problem, but of the supposed forms, only one with a defined genetic cause – type 1 polysaccharide storage myopathy (PSSM1) – is common in the UK. In these animals, diagnosis can readily be achieved by DNA testing (from EDTA blood or hair root plucks). Clinicians should consider carefully the breed of the affected animal, since the prevalence of the mutation in muscle glycogen synthase (*GYS1*) varies considerably between breeds: it is high in Quarter Horses and related breeds and continental European draught breeds, but has not been reported in pure Arabians, Thoroughbreds or Standardbreds. Other postulated disorders, such as so called, PSSM2 and myofibrillar myopathy remain ill-defined; as such, their diagnosis as separate, or defined entities is, in my opinion, open to question. In particular, commercial enterprises offering genetic testing for these disorders have, to date, not had their methodology peer-reviewed in a robust manner, leading me seriously to question the validity of genetic testing for PSSM2 and myofibrillar myopathy. In contrast, evidence now exists refuting the validity of the genetic tests offered for these disorders. It is not surprising that many horse-owners, (and vets) are confused!

Muscle biopsy is an ancillary diagnostic test that is useful in a variety of exertional and nonexertional myopathies, but clinicians should be aware of the information that can be derived from it. In many horses with exertional rhabdomyolysis, in particular, Thoroughbreds, Standardbreds and Arabians, muscle biopsy provides information about the severity and chronicity of the disorder, and confirms what is suspected clinically (i.e. that a myopathy exists). Certain histopathological features can be helpful when suggesting prognosis in athletic animals. Furthermore, confirming that the underlying pathology is compatible with the disorder known as recurrent exertional rhabdomyolysis (and ruling out other rare disorders), might be helpful when selecting prophylaxis or treatment. In other cases, a muscle biopsy can give clues as to the possible pathogenesis, for example with immune-mediated, toxic or infectious conditions. Finally, muscle biopsy can be the optimal way to confirm an underlying myopathy in a horse with occasional or mild elevations in CK or AST activity, or indeed, in a horse that displays other signs compatible with a muscle problem – for example, paresis – but that has normal plasma muscle enzymes. Indeed, very likely in my experience, horses with underlying myopathies are overlooked, simply because they have a normal CK or AST.

In summary, in this presentation I will discuss possible approaches to the laboratory investigation of neuromuscular disorders of horses including the role of muscle biopsy (using fresh (unfixed) samples) for disorders such as exertional rhabdomyolysis, equine motor neuron disease and sarcocytosis, genetic testing (for polysaccharide storage myopathy, malignant hyperthermia, immune-mediated myositis susceptibility and other disorders). I will cover the likely future directions for equine neuromuscular disease laboratory investigation and the limitations and practicalities of laboratory testing for this group of often enigmatic disorders.