PSSM IN HORSES: COMMON BUT UNDER-DIAGNOSED CONDITION?

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Tim Watson considers the clinical signs, diagnosis and treatment of polysaccharide storage myopathy and suggests it may be under-recognised

Summary

Polysaccharide storage myopathy (PSSM) is associated with abnormal accumulation of polysaccharides within skeletal muscle. It is a frequent cause of exertional rhabdomyolysis in horses, accounting for 40 per cent of neuromuscular disease in certain populations, and is particularly common in quarter horse, draught and warmblood breeds, together with their crosses.

The majority of cases carry a mutation in the glycogen synthase 1 (GYS1) gene for which a genetic test is available. Affected horses can remain asymptomatic or present with poor performance, gait abnormalities, muscle stiffness or severe myopathy. Signs are usually precipitated by exercise, especially following a period of rest, and recurrent in occurrence. Mild disease is characterised by a stiff gait, anxiety and stretching out associated with muscle cramps and tremors. More severe cases can become distressed with sweating and reluctance to move. Raised plasma muscle enzymes indicate rhabdomyolysis and PSSM is confirmed by genetic testing of mane hairs or blood. However, not all PSSM cases carry the GYS1 mutation and muscle biopsy may be required to confirm the diagnosis. Following symptomatic treatment an early return to exercise is advised, with gradual increase in duration and intensity. Repeated bouts can be prevented by feeding a high fat/low starch diet and ensuring regular work or turnout.

Key words

polysaccharide storage myopathy, neuromuscular disease, GYS1, rhabdomyolysis

POLYSACCHARIDE storage myopathy (PSSM) is a common and, arguably under-recognised, cause of exertional rhabdomyolysis in horses. It is associated with abnormal accumulation of glycogen and amylase-resistant polysaccharide within skeletal muscle fibres.

Some animals are asymptomatic, whereas others present with signs that include poor performance, gait abnormalities, muscle stiffness or signs of severe myopathy. The majority of cases carry a missense mutation in the glycogen synthase 1 gene (GYS1; McCue et al, 2008a).

Epidemiological studies from the United States have shown PSSM to be the most common diagnosis for horses presenting with a neuromuscular disorder. In a sample of 1,426 muscle biopsies submitted to the University of Minnesota Neuromuscular Diagnostic Laboratory, 572 horses (40 per cent) were found to be affected by PSSM (McCue et al, 2006). While equivalent UK epidemiological data is lacking, the GYS1 gene mutation was found in 21 per cent of Britishbased horses with histories of exertional rhabdomyolysis (Stanley et al, 2009).

What causes PSSM?

The GYS1 mutation identified as a cause of PSSM results in unregulated activity of glycogen synthase and the enzyme responsible for branching of glycogen molecules in muscle. This so-called “gain of function” mutation is coded R309H because of a G to A base substitution that changes the normal arginine (R) at codon 309 to histidine (H; McCue et al, 2008a).

The mutation leads to the production of glycogen with an abnormal three-dimensional structure, which is resistant to the usual processes of utilisation or degradation and accumulates within the cytoplasm of skeletal myocytes. How this accumulation of polysaccharide causes muscle disease is, however, unclear.

Possible mechanisms include physical interference with the contractile apparatus, destruction of affected muscle fibres, or unsuitability of the stored glycogen as an energy substrate.

Not all horses with PSSM have the GYS1 mutation and this has resulted in the classification of two forms of the condition. Horses with type 1 PSSM have one or two copies of the mutant R309H allele, and this is an autosomal dominant condition. Those with type 2 PSSM do not possess the gene mutation, but have the same histopathological features.

Clinical presentation of horses with PSSM is variable and appears to be influenced by genetic factors, an individual’s muscle fibre type composition, and environmental influences such as diet

and exercise. Subclinical disease is common and has been identified in 12 per cent of healthy quarter horses (McCue and Valberg, 2007).

Disease severity in horses with type 1 disease is increased in animals that also harbour a ryanodine receptor mutation (McCue et al, 2009) and is also related to the number of copies of the mutant R309H allele in the GYS1 gene (Naylor et al, 2012). Resting plasma aspartate aminotransferase (AST) and creatine kinase (CK) activities, together with histological measures of PSSM severity, increase according to the number of mutant alleles (Figure 1 and Figure 2).

Who gets PSSM?

Breed variation exists in prevalence of PSSM – of the 572 horses identified with PSSM by McCue et al, 63 per cent were quarter horse-related breeds (Figure 3), 12 per cent draught breeds and nine per cent warmblood breeds (McCue et al, 2006). Estimates of prevalence reveal 54 per cent of draught, 52 per cent to 55 per cent of warmblood and 48 per cent of quarter horse bred horses may be affected (McCue et al, 2006; Hunt et al, 2008). In contrast, prevalence within Thoroughbreds and Arabians was five per cent and three per cent, respectively (McCue et al, 2006).

This pattern of distribution largely reflects differences in the frequency of the GYS1 mutation. To date, it has been identified in more than 20 breeds (McCue et al, 2010), with the highest frequency in continental European draught (62 per cent to 87 per cent) and quarter horse (72 per cent) related breeds (McCue et al, 2008; Baird et al, 2010).

In the UK, it has been identified in a variety of horses including quarter horse, Appaloosa, warmblood, Connemaracross, cob, polo pony and Thoroughbred cross (Stanley et al, 2009). The mutation has not yet been found in Thoroughbreds, Connemaras or Welsh ponies (McCue et al, 2010).

Genetic analysis has confirmed the GYS1 mutation is identical by descent, suggesting it was present before the establishment of diverse breeds (McCue et al, 2008). Frequency of the mutant R309H allele is high and this could be explained by breeding of affected, but asymptomatic, individuals, since signs of PSSM are suppressed by historical managements that include daily work and low starch diet. It is also possible the mutation conferred an evolutionary advantage by promoting storage of glycogen in muscle at times when food was scarce.

Clinical signs and diagnosis

Signs of PSSM are variable but typical of tying-up. Mild episodes are characterised by a stiff gait, anxiety and stretching out – as if trying to urinate – associated with muscle cramping. Owners may complain the horse is “lazy”, or appears to be affected by shifting limb lameness, sometimes with muscle atrophy and paresis. The abdomen may appear tense, with fine tremors visible over the flanks.

More severe disease is typical of acute rhabdomyolysis with painful behaviour, sweating, and reluctance to move or recumbency. Muscles, especially those over the hindquarters, may be hard and painful to palpate. Some horses may appear “colicy”, pawing at the ground and rolling after exercise. Myoglobinuria can be a feature.

Symptoms are often precipitated by exercise, especially when horses begin training or return to work after a period of rest with little turnout. There may be a recurrent pattern, with a history of several episodes that correlates with training or work schedules.

Horses with clinical signs will have elevated plasma AST and CK activities, but enzyme levels may well be normal in asymptomatic cases of PSSM. Taking bloods four to six hours after a submaximal exercise test of two minutes walking and 13 minutes trotting may be helpful in these horses: a CK level greater than 800U/L indicates muscle damage, although not specific for PSSM.

If the case is a quarter horse type, such as an Appaloosa, draught or warmblood, then it is advisable to check for the GYS1 mutation that is common in these breeds. This test is offered by Animal Genetics UK at £25 using samples of hair from the mane. The Comparative Neuromuscular Diseases Laboratory at the RVC also offers a genetic test on blood samples.

In cases of a breed in which the GYS1 mutation is uncommon, such as the Arabian or Thoroughbred, it makes better diagnostic sense to submit a muscle biopsy for histopathological examination. This may also be necessary in cases of type 2 PSSM, where the condition is strongly suspected, but the horse tests negative for the GYS1 mutation. Biopsies should be taken from the semimembranosus or semitendinosus muscle.

Treatment

Initial treatment is the same as for other forms of rhabdomyolysis, including NSAIDs for mild to moderate disease, together with opiate analgesics in more severe cases. Acepromazine has been advocated because of its vasodilatory properties, which helps muscle perfusion, but should be used with caution in patients that are dehydrated. Corticosteroids offer the potential to limit further muscle damage, but their efficacy is unproven. Intravenous fluid therapy may be required in dehydrated horses, to correct hypovolaemia and prevent possible nephrotoxicity associated with myoglobinuria.

Concentrate feeding should be stopped and gentle in-hand walking recommended for mild cases. Turnout in a small paddock is advised as soon as affected horses are moving freely because this will enhance muscle metabolism and improve recovery.

Prevention

Careful attention to diet and exercise is critical to preventing further episodes. Exercise needs to be

reintroduced gradually, starting with no more than five minutes of uncollected walk/trot on a lunge or under saddle, and increasing by two minutes each day up to 15 minutes. From then on, 15-minute intervals should be interspersed by a five minute break at walk. Canter work can be introduced after four weeks of walk/trot. Regular exercise is important and days off should be minimised, with turnout or exercise on a walker offered on rest days.

Dietary interventions are focused on high fat/low starch diets, so metabolism shifts away from the defective glycolytic pathway to the oxidation of fats, with a significant portion of energy coming from fermentable fibre. This results in less glucose uptake into muscle cells, limiting substrate for polysaccharide synthesis, and provides free fatty acids for energy utilisation.

Forages should have nonstructural carbohydrate content (NSC) or starch content of 12 per cent or less. This is because forages with greater than 12 per cent NSC have been shown to exaggerate glycaemia and insulinaemic responses in quarter horses with PSSM, with potentially detrimental elevations in insulin concentrations (Borgia et al, 2011). Hay and haylage are generally appropriate in this respect, but lush grass should be avoided.

Assuming a horse eats two per cent of its bodyweight a day, hay or haylage with 12 per cent NSC will almost meet daily energy requirements for those in light work. Additional calories can be provided in the form of vegetable oil that can be mixed with high fibre cubes or mix. This should be added gradually, starting with a cupfull, and adjusted according to the horse’s weight and exercise tolerance. Alternatively, several feed companies produce high fat/low starch rations that are suitable for all types of competition horses.

References

- Baird J D, Valberg S J, Anderson S M et al (2010). Prevalence of the glycogen synthase 1 (GYS1) mutation causing type 1 polysaccharide storage myopathy in continental European draught horse breeds, *Veterinary Record* **167**: 781-784.
- Borgia L, Valberg S, McCue M et al (2011). Glycaemic and insulinaemic responses to feeding hay with different non-structural carbohydrate content in control and polysaccharide storage myopathy-affected horses, *Journal of Animal Physiology and Animal Nutrition (Berlin)* **95**: 798-807.
- Hunt L M, Valberg S J, Steffenhagen K et al (2008). An epidemiological study of myopathies in Warmblood horses, *Equine Veterinary Journal* **40**: 171-177.
- McCue M E and Valberg S J (2006). Estimated prevalence of polysaccharide storage myopathy among healthy Quarter Horses in the United States, *Journal of the American Veterinary Medical Association* **231**: 746-750.
- McCue M E, Ribeiro W P and Valberg S J (2006). Prevalence of polysaccharide storage myopathy in horses with neuromuscular disorders, *Equine Veterinary Journal Suppl* Aug: 340-344.
- McCue M E, Valberg S J, Miller M B et al (2008a). Glycogen synthase (GYS1) mutation

causes a novel muscle glycogenosis, *Genomics* **91**: 458-466.
- McCue M E, Valberg S J, Lucio M et al (2008b). Glycogen synthase (GYS1) mutation in diverse breeds with polysaccharide storage myopathy, *Journal of Veterinary Internal Medicine* **22**: 1,228-1,233.
- McCue M E, Valberg S J, Jackson M et al (2009). Polysaccharide storage myopathy phenotype in quarter horse-related breeds is modified by the presence of an RYR1 mutation, *Neuromuscular Disorders* **19**: 37-73.
- McCue M E, Anderson S M, Valberg S J et al (2010). Estimated prevalence of the type 1 polysaccharide storage myopathy mutation in selected North American and European breeds, *Animal Genetics* **41** (Suppl 2): 145-149.
- Naylor R J, Livesey L, Schumacher J et al (2012). Allele copy number and underlying pathology are associated with subclinical severity in equine type 1 polysaccharide storage myopathy (PSSM1), *PLoS One* 7: e42317.
- Stanley R L, McCue M E, Valberg S J et al (2009). A glycogen synthase 1 mutation associated with equine polysaccharide storage myopathy and exertional rhabdomyolysis occurs in a variety of UK breeds, *Equine Veterinary Journal* **41**: 597-601.