

Review Article

Polysaccharide storage myopathy – the story so far

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Keywords: horse; PSSM; exertional rhabdomyolysis; GYS1**Summary**

Polysaccharide storage myopathy (PSSM) was first described in 1992 in Quarter Horses, Appaloosa and Paint-related breeds with clinical signs of exertional rhabdomyolysis. The disease is characterised by the accumulation of excessive glycogen and diastase-resistant amylopectin polysaccharide inclusions within skeletal muscle fibres. The discovery of a mutation in the glycogen synthase 1 (GYS1) gene in some, but not all, horses with the disease suggested that PSSM represents a group of diseases with similar pathology but different aetiologies and that the pathogenesis is more complex than initially thought. Type 1 PSSM (PSSM1) refers to horses with the GYS1 mutation and has subsequently been identified in a large number of breeds found in Europe and North America. Clinical presentations associated with PSSM1 can vary and increased muscle enzyme activity at rest or following exercise often accompanies PSSM1; however, such changes may not be present in all cases. A diagnosis of PSSM is made on the basis of histopathology or specifically PSSM1 is diagnosed by genotyping horses for the GYS1 mutation. Cases usually respond well to management changes, in particular a diet low in starch and high in fat when it is accompanied by regular exercise.

Introduction

Exertional rhabdomyolysis is a syndrome of muscle damage usually precipitated by exercise. Once considered a single disease entity, it is now understood to represent a common clinical presentation of several very distinct disease processes (Valberg *et al.* 1999a).

First described by Valberg *et al.* (1992) in Quarter Horse and Appaloosa-related breeds with exertional rhabdomyolysis, polysaccharide storage myopathy (PSSM) has subsequently been identified in a number of different breeds found in Europe and the United States (Valentine *et al.* 2000; McCue *et al.* 2006).

Polysaccharide storage myopathy is characterised by the accumulation of excessive glycogen and diastase-resistant amylopectin polysaccharide inclusions within skeletal muscle fibres (Valberg *et al.* 1992) (**Fig 1**). Unlike normal glycogen stored in muscle fibres, these polysaccharide inclusions are resistant to digestion with diastase and therefore are not broken down in the normal manner. The discovery of a mutation in the glycogen synthase 1 (GYS1) gene in some, but not all, horses with the disease (McCue *et al.* 2008a) suggested that PSSM is in fact a group of diseases of different aetiologies and that the pathogenesis is more complex than initially thought. As not all horses with PSSM possess the GYS1 mutation (McCue *et al.* 2008a), this led to the disease being reclassified as type 1 PSSM (PSSM1), referring to individuals that possess the

gene mutation and type 2 PSSM (PSSM2) for individuals that have the characteristic histopathology in their skeletal muscle but do not possess the mutant allele. Many of the earlier studies of horses with PSSM performed by Dr Valberg and coworkers are now understood to have involved horses with the GYS1 mutation and therefore refer to PSSM1 (S.J. Valberg, personal communication). It remains possible that the polysaccharide inclusions in horses with PSSM2 may be a common endpoint of several different pathological processes. As more is understood about this subset of horses without the GYS1 mutation, several abnormalities of glycogen metabolism may be identified and this group subdivided further, as with human glycogen storage diseases. This paper reviews our current understanding of type 1 PSSM (PSSM1; horses with the GYS1 mutation) for which a definitive test is currently available.

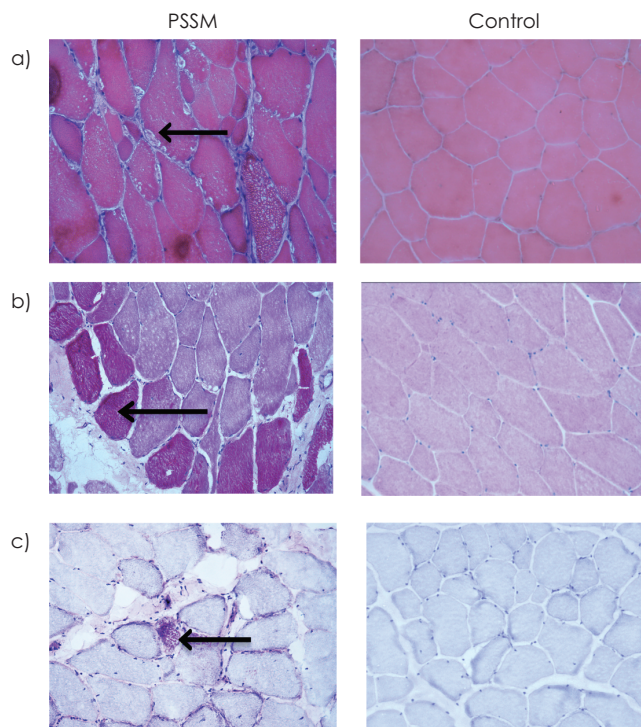


Fig 1: Characteristic skeletal muscle histopathology in type 1 PSSM compared with muscle from a matched control stained with a) haematoxylin and eosin showing sub-sarcolemmal vacuolation (arrow) and marked variation in fibre size, b) periodic acid schiff (PAS) showing increased glycogen accumulation (arrow) and c) periodic acid schiff following predigestion with diastase revealing abnormal diastase-resistant polysaccharide (arrow). $\times 20$ magnification.

Skeletal muscle pathology

Histopathology of muscle from horses with PSSM1 reveals excessive glycogen alongside abnormal nonlysosomal bound polyglucosan bodies containing less highly branched glycogen with protein aggregates (Valentine *et al.* 2001; Annandale *et al.* 2004; McCue *et al.* 2009a). The presence of subsarcolemmal vacuoles, predominantly in type 2 muscle fibres (those with a propensity for glycolytic metabolism) are also a common finding (Valberg *et al.* 1992) (**Fig 1**). No disruption of the important membrane associated protein dystrophin has been identified in affected horses (Naylor *et al.* 2012a). Nonspecific chronic myopathic changes such as internalised nuclei and variation in muscle fibre size are consistent with previous muscle damage and regeneration. Affected horses also have a shift in muscle fibre type from type 2x to type 2a fast twitch fibres (Naylor *et al.* 2012a). As the disease affects type 2 muscle fibres, muscles that contain a high proportion of these fibres such as the semimembranosus or gluteal muscle are usually selected for biopsy. The severity of histopathological abnormalities will likely reflect the fibre type proportion of a particular muscle. It is intriguing that similar muscle pathology has recently been described in a large number of marine mammals although, unsurprisingly, the clinical histories for these species are unknown (Sierra *et al.* 2012).

How the characteristic polysaccharide inclusions relate to the clinical signs in patients with PSSM is unclear. There is evidence to support a metabolic defect leading to a reduction of energy availability within affected muscle fibres (Annandale *et al.* 2005). This may explain the observation of clinical signs in young foals with the disease in the absence of extensive change on muscle biopsy (Byrne *et al.* 2000; De La Corte *et al.* 2002). Therefore, the polysaccharide inclusions may be a coincidental marker of the disease rather than causative. In addition, it has been proposed that the physical presence of the polysaccharide inclusions and subsarcolemmal vacuoles may disrupt the arrangement and function of the myofibrillar proteins and their attachments, a theory supported by the correlation between the severity of histopathology and muscle enzyme activity (Naylor *et al.* 2012a). It is difficult to reconcile the clinical improvement observed in response to management changes if physical interference was solely responsible for the clinical signs observed, as the polysaccharide inclusions do not change with such husbandry modifications.

Aetiology of PSSM

In contrast to Thoroughbred horses with recurrent exertional rhabdomyolysis (RER) no abnormality of muscle contracture was detected in *in vitro* studies of muscle from horses with PSSM, suggesting a different pathogenesis of the 2 diseases (Lentz *et al.* 1999). The absence of any derangement in the ability of affected horses to utilise glycogen or produce lactate during exercise led to the suggestion that PSSM results from abnormal glycogen storage rather than a defect affecting glycogen utilisation (Valberg *et al.* 1999b). This is also supported by the finding that the greatest increases in CK activity were observed in PSSM horses performing submaximal rather than maximal exercise (Valberg *et al.* 1999b). Studies evaluating the role of insulin sensitivity in this abnormal glycogen storage disease have yielded conflicting results in different breeds of horses (Annandale *et al.* 2004; Firshman

et al. 2008). Quarter Horses with PSSM were shown to have increased insulin sensitivity relative to control horses (De La Corte *et al.* 1999a; Annandale *et al.* 2004), whilst no difference was found between Belgian draught horses and controls (Firshman *et al.* 2008). These differences may reflect inherent breed differences in other genes regulating insulin sensitivity or differences in muscle fibre type proportions (Firshman *et al.* 2008) suggesting that mechanisms other than heightened insulin sensitivity may be resulting in the accumulation of abnormal polysaccharide within skeletal muscle of some horses with PSSM1.

There are 11 skeletal muscle glycogenoses recognised in man, many of which produce histopathological features similar to PSSM. These diseases are associated with autosomal recessive defects in specific enzymes of glycogen metabolism, lysosomal abnormalities or defects of AMP-dependent protein kinase (DiMauro and Lamperti 2001). The clinical phenotypes observed in some of these diseases are similar to those seen in horses with PSSM1. Initial work into PSSM in the horse logically focused on evaluating the activity of these key enzymes in affected horses; however, no abnormalities were identified (Valberg *et al.* 1998). Similarly, no difference in the content of the major insulin sensitive glucose transporter GLUT4 in muscle from affected horses was found (Annandale *et al.* 2004), although more recently many more GLUT receptors have been identified in the skeletal muscle of horses, such as GLUT8 and GLUT12 (Lacombe 2014) and their role in PSSM is yet to be evaluated.

Enhanced glycogen synthesis was suggested when horses with PSSM were shown to resynthesise glycogen more rapidly following exercise depletion than normal horses (De La Corte *et al.* 1999b). As normal glycogen synthesis is under the control of 2 enzymes (glycogen synthase and glycogen branching enzyme) an alteration in the activity of one of these enzymes would likely affect the relative branching of the glycogen molecule formed leading to an altered 3-dimensional structure (Annandale *et al.* 2004) that may impart a resistance to digestion with diastase.

Type 1 PSSM

In 2008, an autosomal dominant, gain of function, mis-sense mutation (R309H) in the glycogen synthase 1 gene (*GYS1*) was identified in association with many but not all cases of PSSM (McCue *et al.* 2008a). Glycogen synthase is an enzyme responsible for the production of glycogen, by joining glucose monomers via alpha 1,4 linkages, under the influence of insulin and glucose-6 phosphate. This point mutation leads to a single amino acid substitution, from arginine to histidine that results in increased glycogen synthase activity (McCue *et al.* 2008a).

To date, the *GYS1* mutation has been identified in a large number of breeds across Europe and North America (McCue *et al.* 2008b, 2009a, 2010; Herszberg *et al.* 2009; Stanley *et al.* 2009b; Baird *et al.* 2010; Jöhlig *et al.* 2011; Schwarz *et al.* 2011) (**Table 1**). A particularly high prevalence has been identified in Quarter Horses, Percheron and Belgian draught horses (McCue *et al.* 2008b), whilst to the authors' knowledge it remains to be identified in a purebred Thoroughbred horse. Given that genotyping affected horses has only been commercially available for the last 5 years, it is highly likely that as more cases are genotyped we can expect to find the mutation in a greater range of breeds. The particularly high prevalence in hardy draught breeds led some authors to suggest that the disease phenotype may have imparted an

TABLE 1: Breeds in which the GYS1 mutation has been identified to date

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

evolutionary advantage in these breeds, which is partly supported by a recent hereditary study (McCoy *et al.* 2014).

Clinical presentation

Whilst there is a distinct correlation between the GYS1 genotype and severity of histopathology (Naylor *et al.* 2012a), there remains considerable variation between the clinical signs associated with PSSM1, from exertional rhabdomyolysis to vague signs of poor performance, suggesting that other genetic and environmental factors may act to modify the disease phenotype (Valberg *et al.* 2011). McCue and coworkers have shown that the ryanodine receptor (RYR1) mutation associated with malignant hyperthermia leads to a more severe phenotype in Quarter Horses with PSSM1 (McCue *et al.* 2009b), whilst environmental factors such as diet and exercise are known to attenuate clinical signs (Firshman *et al.* 2003; Ribeiro *et al.* 2004; Borgia *et al.* 2010). It is plausible that many of the previously suggested acquired causes of rhabdomyolysis, such as hormonal imbalances or antioxidant deficiencies, may exert an effect by modifying the phenotype of an already genetically susceptible individual.

Whilst many horses with PSSM1 are asymptomatic (Johlig *et al.* 2011; Naylor *et al.* 2012a), exertional rhabdomyolysis is the most commonly and perhaps easily recognised clinical syndrome. Exertional rhabdomyolysis was reported in over 90% of affected cases in one study of horses where biopsies were obtained to investigate poor performance (McCue *et al.* 2009a). In one family of Warmblood horses, 59% of those with the GYS1 mutation also had a history of exertional rhabdomyolysis (Johlig *et al.* 2011) and those with the mutation were 7.1 times more likely to show signs of exertional rhabdomyolysis than those without. However, more subtle clinical signs may easily be overlooked and these include

poor performance, muscle fasciculations, muscle atrophy, gait abnormalities, generalised or pelvic limb stiffness, undiagnosed lameness, paresis or back pain (Quiroz-Rothe *et al.* 2002; McCue *et al.* 2009a). Interestingly, PSSM-affected horses are often described as having a calm demeanor (Valberg *et al.* 2011).

Shivers

Early reports suggested a possible link between PSSM and the incidence of shivers, a neuromuscular condition characterised by a reluctance to lift the pelvic limbs and to back-up, often associated with fasciculations of the musculature of the pelvic limb and tail (Firshman *et al.* 2005). This was supported by the high prevalence of weakness in horses with PSSM and a report of 2 Belgian horses with weakness and shivers that were diagnosed with severe PSSM on histopathology of skeletal muscle at *post mortem* examination (Valentine *et al.* 1999). However, no association between the 2 conditions was identified in 2 larger studies of 103 Belgian draught horses (Firshman *et al.* 2005) or 132 Warmblood horses (Hunt *et al.* 2008). It appears that both PSSM and shivers are neuromuscular disorders that commonly occur in similar breeds of horses, occasionally concurrently and that there is no causative relationship.

Cardiac disturbances

Human glycogenoses are often associated with specific cardiac phenotypes that contribute to exercise intolerance. In particular, enhanced atrioventricular conduction leading to arrhythmogenesis and cardiac failure are seen (Arad *et al.* 2005; Soliman *et al.* 2008). Given that polysaccharide inclusions have been reported in the myocardium of affected horses at *post mortem* examination (Valentine *et al.* 1997, 2001; Larcher *et al.* 2008) and that sudden death has been described in horses with PSSM, further investigation of the cardiac phenotype of horses with PSSM1 was performed (Naylor *et al.* 2012b). No significant structural changes or arrhythmias were detected in affected horses when compared with matched controls (Naylor *et al.* 2012b).

Diagnosis

Resting muscle enzyme activity may be used to screen for subclinical muscle damage in possible PSSM1 cases; however, increases in basal creatine kinase (CK) and aspartate transferase (AST) activity may not be observed in affected horses, particularly in those that are heterozygous for the GYS1 mutation (Naylor *et al.* 2012a). Measuring skeletal muscle enzyme activity following 20 min of submaximal exercise (e.g. trot and canter work) may increase the sensitivity of this assessment, particularly for horses with signs of exercise intolerance (Valberg *et al.* 1999b). A significant difference was observed between horses with PSSM1 and controls in CK activity at 4 h post exercise but not AST activity 4 or 24 h post exercise in one study of Belgian draught horses (Naylor *et al.* 2012a), whereas significantly higher post exercise AST activities were observed in horses with PSSM1 relative to controls in an earlier study of Haflinger horses (Schwarz *et al.* 2011). These studies suggest that there may be breed differences in muscle enzyme responses to exercise in horses with PSSM1 or may simply reflect small sample sizes. Furthermore, the changes in muscle enzyme activity following exercise may be relatively small (increases of less than 50% above resting levels)

compared with those typically seen in other diseases such as RER and importantly there is considerable overlap between the response of unaffected control horses and those heterozygous for the *GYS1* mutation. Therefore, raised muscle enzyme activity should increase the index of suspicion of a myopathy and prompt further investigations such as muscle biopsy or *GYS1* genotyping. However, PSSM cannot be excluded in the absence of large changes of muscle enzyme activity following exercise.

A diagnosis of PSSM has traditionally been made on histopathology of muscle biopsy samples; however, this technique is unable to clearly differentiate between PSSM1 and PSSM2. The identification of the *GYS1* mutation has allowed the development of a restriction fragment length polymorphism (RFLP) assay to diagnose *type 1* PSSM (McCue *et al.* 2008a). This is performed on DNA extracted from EDTA whole blood samples or hair roots (approximately 30 required which are easily collected from the mane or tail). This assay is a less invasive method for testing for PSSM1 than the traditional muscle biopsy and is particularly useful in breeds known to have a high prevalence of the *GYS1* mutation. The blood test may also be useful in younger individuals where changes on histopathology are fewer, as it is known that the severity of the polysaccharide accumulations increases as an animal ages (De La Corte *et al.* 2002). Furthermore, genotyping affected animals may provide useful prognostic information for making decisions with regards to training and breeding as it has been shown that the severity of the skeletal muscle pathology correlates with the number of copies of the mutant allele with homozygotes having more severe histopathology than those heterozygous for the *GYS1* mutation (Naylor *et al.* 2012a).

It is often useful to consider the breed of the animal when deciding which diagnostic test(s) to perform. In breeds with a particularly high prevalence of PSSM1, such as draught and Quarter Horse-related breeds, it may be preferable to genotype the horse for the *GYS1* mutation initially. A particularly high prevalence is found in continental European breeds such as the Percheron, whilst the prevalence in UK derived breeds such as the Clydesdale or Shire is much lower (McCue *et al.* 2010). Conversely, in breeds with a lower prevalence of the *GYS1* mutation, such as Cobs and Welsh ponies or indeed those where the mutation has yet to be described such as Thoroughbred horses that would more likely have PSSM2 or another myopathy, a skeletal muscle biopsy remains the most appropriate diagnostic test currently available. Skeletal muscle biopsy samples should be harvested from the gluteal or semi-membranosus muscles and are easily obtained from the standing sedated animal (Ledwith and McGowan 2004). Biopsy samples are best preserved when placed in an empty sterile pot and transported immediately on ice packs to the laboratory (Stanley *et al.* 2009a). It is recommended to liaise with the diagnostic laboratory prior to collecting the biopsy and avoid posting samples at the end of the week to avoid unnecessary delays in transport.

Treatment of PSSM

The aim of managing horses with PSSM is to limit the constant synthesis of glycogen within skeletal muscle by reducing circulating insulin and promoting glycogen metabolism through regular exercise. In addition, an alternative energy source such as fat can be provided as long as the horse is not overweight. These recommendations are based on research performed in horses with PSSM1. To date, there are no

controlled studies in horses with PSSM2 although it is assumed that similar recommendations apply. Regular daily exercise in addition to pasture turnout is advised, in conjunction with a diet low in starch and sugar (<10% digestible energy [DE] as nonstructural carbohydrates [NSC]) and relatively high in fat (13–20% DE) (Ribeiro *et al.* 2004; Borgia *et al.* 2010). Horses should continue to receive 1–2% of their body weight as forage, ideally with a low (<12%) NSC content (Borgia *et al.* 2011) and in some cases, depending on workload and energy requirements, further caloric supplementation may not be required. Grazing may need to be restricted at certain times of the year when the NSC content of grass is particularly high. There are specifically formulated commercial diets available (Dodson and Horrell ERS Pellets¹ or Saracen Releve²), although adequate fat will only be provided if fed in quantities recommended by the manufacturers. Alternatively, a low starch diet may be supplemented with vegetable oil, up to a maximum of 1 ml/kg bwt to provide sufficient calories. In some cases, diets with a slightly lower fat content may be more palatable yet still be sufficient to control the condition. A high lipid diet increases the requirement for antioxidants and therefore a feed balancer containing vitamin E may be beneficial.

The prognosis is favourable in cases where dietary and exercise recommendations are followed and these horses are significantly more likely to have an improvement in the severity and frequency of clinical signs relative to those cases where only one (exercise of dietary) recommendation is followed (Firshman *et al.* 2003). A clinical improvement may be observed within 6 weeks, although complete adaptation to these diets likely takes several months (Ribeiro *et al.* 2004).

Type 2 PSSM

Horses with PSSM2 are not easily distinguishable from those with PSSM1 on the basis of clinical signs and histopathology, although subtle differences in the morphological appearance of polysaccharide inclusions have been suggested (McCue *et al.* 2009a). Fine granular, often diastase negative, inclusions are frequently located close to the sarcolemma in PSSM2 as opposed to the coarse granular diastase positive granules frequently observed in PSSM1 (McCue *et al.* 2008a, 2009a). *Type 2* PSSM may be a result of one sole enzymatic defect or perhaps more likely may reflect a group of glycogen storage diseases, with a similar histopathological endpoint. Further work is needed to further elucidate the pathophysiological process(es) involved in these horses.

Conclusion

Polysaccharide storage myopathy is a disease seen in a variety of breeds throughout the UK and Europe as well as North America. The particularly high prevalence of PSSM1 in some draught breeds likely reflects a prior evolutionary advantage. The recent identification of the *GYS1* mutation could allow for eradication of the disease from these breeds by the implementation of coordinated breeding programmes. However, this remains controversial in those breeds with a low incidence of clinical signs. The clinical presentation can vary as can muscle enzyme activity in affected horses, therefore muscle biopsy and genotyping for the *GYS1* mutation is required to establish a definitive diagnosis. Whilst no specific treatment is currently available affected horses usually respond well to management changes, in particular a low

starch high fat diet in conjunction with regular exercise. With appropriate management the prognosis is favourable.

Author's declaration of interests

No conflicts of interest have been declared.

Manufacturers' addresses

¹Dodson and Horrell Ltd, Kettering, Northamptonshire, UK.

²Saracen Horse Feeds, Aylesford, Kent, UK.

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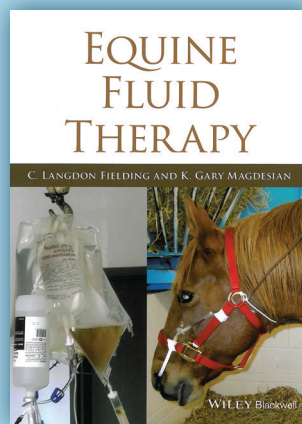
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