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Review Article

The Interplay of Genetics, Exercise, and Nutrition in Polysaccharide Storage Myopathy

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A B S T R A C T

Polysaccharide storage myopathy (PSSM), identified in 1992 in a subset of horses with exertional rhabdomyolysis, is a glycogenosis characterized by amylase-resistant polysaccharide in a small number of skeletal muscle fibers along with 1.5 to 4 times normal muscle glycogen. Extensive biochemical and physiological analyses failed to identify defects in glycogenolysis and glycolysis. In 2008, a genome-wide association analysis detected a locus on equine chromosome 10 that was strongly associated with the PSSM in Quarter Horses. Glycogen synthase 1 (GYS1), which encodes the skeletal muscle isoform of glycogen synthase (GS), was a strong candidate gene for PSSM based on its location on equine chromosome 10. Sequencing of the *GYS1* gene in PSSM and control Quarter Horses identified only one single base-pair change that resulted in an amino acid substitution in the GS enzyme. Mean GS activity was higher in PSSM than control muscle homogenates in both the presence and absence of the allosteric activator glucose 6-phosphate, suggesting that the GS enzyme in horses with PSSM is constitutively active. High-grain diets increase serum insulin concentrations which further act to stimulate GS activity. An restriction fragment length polymorphism assay for the *GYS1* mutation showed that 10% of the Quarter Horse breed and a minimum of 20 other breeds have the *GYS1* mutation. Muscle biopsies obtained after 20 minutes of aerobic exercise revealed much higher inosine monophosphate concentrations and lower adenosine monophosphate in whole muscle and single fibers from PSSM as compared with control horse muscle. Thus, the *GYS1* mutation responsible for PSSM seems to cause an energy imbalance exacerbated by high-grain diets, which results in adenine nucleotide degradation in individual muscle fibers of horses with PSSM during submaximal exercise.

1. Introduction

Exertional rhabdomyolysis (ER), literally the dissolution of muscle with exercise, has been a common cause of disability in many breeds of horses for more than a century. During acute episodes, horses exhibit clinical features of muscle stiffness, cramping, sweating, and reluctance to move forward. For many decades, it was assumed that there was one cause for this condition because clinical signs were very similar among acutely affected horses. However, after the muscle biopsy technique was introduced to equine medicine, it became clear that there are many distinct causes for ER which differ by molecular or environmental bases, recurrence, prognosis, and responses to management changes [1]. One distinct cause of ER is polysaccharide storage myopathy (PSSM). This condition was first recognized in afflicted Quarter Horses that had high muscle glycogen concentrations and accumulation of abnormal polysaccharide in muscle cells [2]. Of note, 60 years earlier, Carlström had also reported an association

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between ER in Draft horses and increased muscle glycogen storage [3]. Terms such as Monday Morning Disease and Holiday Disease were used to describe this Draft horse disease because its expression was linked to a period of rest on a high-grain diet before the inciting bout of exercise.

2. Terminology

Several acronyms have been used for polysaccharide storage myopathy besides PSSM, including equine polysaccharide storage myopathy, and debate exists as to whether these acronyms encompassed one muscle condition [4-6] or different conditions [1]. Glycogen is a highly branched polymer that is sensitive to digestion by the enzyme amylase. In the original group of horses diagnosed with PSSM, an increase in normal amylase-sensitive glycogen was discovered along with an abnormal amylase-resistant polysaccharide [2,7]. Valberg proposed amylase-resistant glycogen as the gold standard for diagnosis of PSSM, whereas others felt that an increase in amylase-sensitive glycogen without the presence of amylase-resistant glycogen should suffice for the diagnosis of PSSM [4,8,9]. The issue was clarified in 2008 when a genetic mutation was identified in horses with amylase-resistant polysaccharide in skeletal muscle [10]. Genetic testing of hundreds of horses that were previously diagnosed with PSSM by muscle biopsy revealed that the vast majority of cases of PSSM characterized by amylase-resistant polysaccharide in skeletal muscle had the same genetic mutation [11]. However, some cases previously diagnosed with PSSM by muscle biopsy, particularly those with amylase-sensitive glycogen, did not possess this genetic mutation, suggesting that there are a minimum of two forms of PSSM [11]. For clarity, the form of PSSM caused by the identified *GYS1* genetic mutation is termed as **type 1 PSSM,** whereas the form of PSSM that is not caused by this mutation and whose origin is yet unknown is now termed as **type 2 PSSM** [12]. In retrospect, much of the scientific studies performed by our research group on PSSM used horses with type 1 PSSM. This review derived from scientific studies of horses with type 1 PSSM will summarize the interplay among the genetic mutation, muscle metabolism, nutrition, and exercise.

3. Acute Clinical Signs

Although some horses with type 1 PSSM are asymptomatic, many develop clinical signs on average at 6 years of age (range, 1-14 years). In general, owners describe horses with type 1 PSSM as having a calm demeanor. Acute signs often develop after $<$20 minutes of light exercise and include tucking up of the abdomen, fasciculations in the flank, muscle stiffness, sweating, reluctance to move forward, and overt muscle contractures. The hindquarters are frequently most affected, but back muscles, abdomen, and forelimb muscles may also be involved. Affected Quarter and Paint Horse foals and weanlings may develop rhabdomyolysis without exercise. During an acute episode of ER, horses with type 1 PSSM often have markedly elevated serum creatine kinase (CK) activity of $>$35,000 U/L and myoglobinuria may be present. Horses that are unfit at the commencement of training, have had a substantial period of rest, or are consuming a diet high in nonstructural carbohydrates (NSC) are most susceptible. Some owners report a seasonal incidence to the development of acute clinical signs, which some have attributed to quality of grass available at the time.

3.1. Chronic Clinical Signs

3.1.1. Light Breeds

Chronic signs of type 1 PSSM in riding horses include a lack of energy when under saddle, reluctance to move forward, stopping and stretching out as if to urinate, and a sour attitude toward exercise [13]. The range of severity of clinical signs of PSSM can be wide. Serum CK activities are often elevated in untreated Quarter Horses, even when horses are rested.

3.1.2. Draft Horse, Draft Crosses, and Warmbloods

The average age of Draft horses diagnosed with PSSM is about 8 years of age [14]. Many Draft horses with PSSM are asymptomatic [14]. Signs of severe rhabdomyolysis and myoglobinuria may occur in horses fed with high-grain diets, exercised irregularly with little turn out, or in those that undergo general anesthesia [15]. Other signs of PSSM in Draft horses include progressive weakness and muscle loss, resulting in difficulty in rising in horses with normal serum CK activity. Gait abnormalities, such as excessive limb flexion, fasciculations, and trembling, are also reported in Draft horses. Although the condition shivers was previously attributed to PSSM, a recent study found no causal association between these two conditions [14]. The median serum CK and aspartate transaminase activities in Draft horses from which biopsies were sent to the University of Minnesota were 459 and 537 U/L, respectively.

4. Pattern of Inheritance

A predilection for certain breeds and familial tendency within breeds introduced the possibility that PSSM was inherited. A small breeding trial of four horses combined with pedigree analysis of $>$20 Quarter Horses with PSSM initially pointed to a recessive pattern of inheritance for PSSM [16,17]. Conclusions were based on the fact that foals from PSSM $\times$ PSSM matings developed PSSM and consanguinity was present in pedigrees. Further expansion of this breeding herd by outcrossing Quarter Horses with PSSM to normal stallions indicated that a dominant pattern of inheritance was most likely because the affected foals arose from mating affected to normal horses [10].

5. Energy Metabolism in Horses with PSSM

5.1. Purine Nucleotides

Horses with PSSM most commonly develop clinical signs of muscle pain and stiffness and elevations of serum CK activity with 15 to 20 minutes of light aerobic exercise [13]. Aerobic metabolism is stimulated when exercise decreases the ratio of adenosine-5'-triphosphate (ATP): adenosine diphosphate (ADP). However, if aerobic or anaerobic metabolism cannot effectively restore this ratio, the myokinase reaction produces ATP and adenosine