

Equine Polysaccharide Storage Myopathy - Keeping up with Evolution

PSSM, EPSM, EPSSM – Oh, give it a name, already!

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Muscle disease in horses, especially Draft horses, has been recognized for well over 100 years. The condition termed “Monday morning disease” was recognized in Draft horses in the days when horses performed the everyday duties now performed by cars, trucks, and tractors. Horses worked long hours, usually six days a week. When given a day of rest on Sunday and provided with a full ration of grain, these horses were prone to massive muscle injury when put in harness on Monday morning. Although it was recognized for years that Monday morning disease (MMD) involved a high grain ration and lack of exercise, decreasing grain and providing daily exercise were no guarantee that this disorder might not still occur. These days MMD is less common in the horse population, probably because they are not asked to perform the same amount of work as their predecessors (although it is still seen in the occasional Amish working Draft or pulling horse). The recognition that MMD reflects an underlying myopathy rather than being simply a management problem has resulted in a whole new way of looking at horses with muscle disorders [1]. But back then, Monday morning disease was lumped into a broad category of exertional muscle disorders, medically termed exertional rhabdomyolysis or ER. For more specific information about exertional rhabdomyolysis, or tying up syndrome, see *Exertional Rhabdomyolysis – Keeping up with Evolution*, in this series of articles.

Although the pathologic findings characteristic of the disease now called **equine polysaccharide storage myopathy (EPSSM)** had been described sporadically in the veterinary literature, those early studies of muscle disorders and the evaluation of muscle biopsies didn't seem to hold any unifying theories. In 1979, Cardinet and Holliday recognized a myopathy associated with abnormal storage of glycogen in an Arabian crossbred horse with exercise intolerance [2]. In 1986, Andrews reported subsarcolemmal masses of storage carbohydrate in the muscle tissue of a Quarter Horse with chronic ER [3]. In 1993, Hulland described an equine myopathy with storage of an abnormal carbohydrate that resulted in sudden onset of recumbency and inability to rise in a Percheron Draft horse [4]. It was not until 1992 when Valberg *et al.* published their landmark paper in the human journal *Neuromuscular Disorders* that **polysaccharide storage myopathy (PSSM)** was recognized to underlie recurrent exertional rhabdomyolysis (ER) in a particular group of Quarter Horse-related breeds [5]. Valentine [6, 7] then reported on an **equine polysaccharide storage myopathy (EPSM)** in Draft horses with a wider range of clinical signs that included severe ER, recumbency with inability to rise, progressive weakness with muscle atrophy, abnormal pelvic limb gait, and post-anesthetic myopathy. This finding led Valentine *et al.* to investigate more Draft-related horses and it soon became clear that such horses were easy to find, and the laboratory changes of EPSSM were readily identified in most muscle biopsies from these horses. Of particular interest was the finding that ‘Shivers’, a progressive hind limb gait abnormality described most commonly in Drafts, was also associated with findings of EPSSM in muscles [6, 8]. The increasing awareness of this metabolic disorder bred a greater understanding of the range of clinical signs possible, breeds affected, and incidence of occurrence. In some of these breeds, the prevalence appears particularly (and surprisingly) high - up to 86% has been reported in Draft-related breeds [9]. Continued studies have confirmed the wide range of clinical signs in affected Draft horses [10] and have gone on to recognize a very similar, if not identical, disorder affecting many other breeds [11, 12, 13, 14], including Arabians, Standardbreds, Morgans and Welsh pony-related breeds [15]. The two different acronyms that have been applied to this disorder are **PSSM** in Quarter Horses (by Valberg) and **EPSM** in Draft breeds (by Valentine). It would appear that each group was published at about the same time. As there is no proof that these are different disorders, and given that this disorder has been found in Draft-QH crossbreds with ER (Valentine, unpublished), the acronym **EPSSM**, for **equine polysaccharide storage myopathy**, was deemed an appropriate compromise.

Many factors, including genetics, temperament, diet, and exercise, determine if and when clinical signs appear. Signs of muscle dysfunction due to EPSSM can occur in horses younger than 1 [16, 17] or older than 20 years [10]. Many different clinical signs occur as manifestations of EPSSM. All manifestations can be related to skeletal muscle dysfunction that results in pain, weakness, stiffness, spasm, atrophy, or any combination of these. Abnormal pelvic limb gait is the most commonly reported problem in EPSSM horses [14]. Abnormalities range from a stiff short-strided gait, to unexplained lameness, to obvious mechanical lameness such as the abnormal flexion of one or both hind limbs characteristic of ‘Shivers’ [10, 11, 14, 18]. Poor performance and/or exercise intolerance can be associated with EPSSM [2, 5, 10, 14, 18]. Muscle atrophy, either generalized or confined to the pelvic limb musculature, is also common [5, 10, 14]. The atrophy of EPSSM is symmetrical, which helps to distinguish it from other causes of muscle atrophy. Horses may be described by owners as having poor musculature of the top-line and/or rump despite rigorous conditioning exercise, and may mimic equine motor neuron diseases. The most obvious sign of muscle dysfunction is ER. This is when exercise, which may actually be relatively minimal, results in severe pain, stiffness of gait and muscle swelling. The muscles most severely affected are the powerful rump, thigh, and back muscles. Other manifestations of EPSSM include back soreness, difficulty trimming and shoeing rear hooves, behavior problems under saddle, and episodic spasmodic colic [14]. Persistent back pain as the sole manifestation of EPSSM has recently been recognized in show jumpers and dressage horses of several breeds [19].

Serum chemistry analysis of the muscle enzymes creatine kinase (CK) and aspartate aminotransferase (AST) sampled 4-6 hours after exercise may reveal increased activities of these enzymes indicative of muscle fiber necrosis [5, 11, 12, 13, 14, 17]. Increases can be very mild or substantial, and horses may or may not show clinical signs of muscle dysfunction at the time of testing.

Other manifestations of EPSSM may be related to muscle pain, stiffness, spasm, or weakness, without overt muscle fiber necrosis and therefore without increases in serum CK or AST. Whatever the reason for this variability, these studies point out one very important feature of enzyme levels in blood. These enzymes are cytoplasmic enzymes, meaning that they are released only when muscle membranes are damaged. As such, they are only indicators of muscle integrity and they are not indicators of muscle function. Muscle may be weak and dysfunctional without being necrotic or damaged. Other diagnostic tests, including blood and urine electrolyte levels and blood vitamin E and selenium concentrations, help to distinguish EPSSM from other disorders, but rarely contribute directly to its diagnosis.

Until recently, the best diagnostic test for EPSSM was examination of a muscle biopsy for characteristic changes of glycogen and complex polysaccharide storage. The “gold standard” laboratory test for this disorder has been the demonstration of amylase- (or diastase) resistant inclusions in skeletal muscle fibers stained with periodic acid Schiff (PAS) reagent, a chemical that stains both glycogen and other complex polysaccharides. Because amylase digests away normal glycogen deposits, inclusions that stain positively with PAS after amylase digestion are regarded as abnormal. Handling of the biopsy specimen, however, had become a point of controversy. There is no doubt that preparation of high quality frozen sections of unfixed muscle samples is the superior method for pathologic evaluation of muscle. This procedure requires keeping a fresh sample suitably moist and cold during overnight shipment to the appropriate laboratory. Samples improperly packed or delayed in shipment resulted in samples unsuitable for evaluation. Glycogen breaks down quickly and PAS stains of frozen sections from mailed-in specimens were often difficult to evaluate. Glycogen staining in frozen sections varies greatly depending on how the sample was handled and how long it took to get to the laboratory to be frozen. Subtle changes in glycogen or cellular architecture could be obscured by shipping on dry ice, thawing, and re-freezing of samples on arrival at the laboratory [20]. And since the characteristic lesions of EPSSM were never evenly distributed within the muscle, careful searching of multiple sections was necessary to find them.

With proper sample and sample processing, it was possible to diagnose specific neuromuscular disorders on formalin-fixed (instead of frozen) sections stained with PAS stain for glycogen [18], but there could be handling errors here too. PAS staining is a routine part of frozen section histochemistry of muscle, but is not considered a routine stain for formalin-fixed muscle, so it must be specifically requested. Inadequate PAS staining procedure can result in a false negative, or under-diagnosis. Overall, glycogen staining is not preserved in formalin-fixed specimens as well as in ideally prepared frozen section, but this may confer an advantage to the pathologist that is similar to the procedure of freezing, thawing, and re-freezing. That is, the loss of some normal glycogen may make abnormal aggregates of glycogen easier to identify.

In all muscle biopsies of horses diagnosed with EPSSM, the aggregates of complex polysaccharide and/or glycogen are accompanied by some degree of chronic muscle tissue change, including increased muscle fiber size, vacuoles, and the presence of internal nuclei within myofibers. Regardless of these technical challenges, it still seems when using the strictest criteria (i.e., the presence of amylase-resistant inclusions in myofibers), EPSSM was being diagnosed in many non-Quarter horse, Warmblood or Draft-related breeds, including Arabians, Morgans, Standardbreds, and Welsh-pony related breeds [15], Andalusians [19], Tennessee Walkers, Thoroughbreds, and Paso Fino horses [Valentine, unpublished]. Using the less stringent pathological criteria (i.e., the presence of abnormal aggregates of glycogen) evidence of EPSSM has been found in other breeds too, including American Saddlebreds, various crossbreds, and American miniature horses.

The pathophysiology of EPSSM is believed to be associated with an abnormality of muscle glycogen metabolism, partly because increased glycogen concentrations are identified within the muscle of affected horses [21]. Normally glycogen acts as a carbohydrate store within muscle, where it is broken down to provide substrate for the glycolytic pathways. Mutations within, or absence of, enzymes involved in these pathways can cause glycogen storage diseases in other species [22]. So, is EPSSM in horses an enzyme defect in either glycolysis or glycogenolysis? A heritable disorder? A genetic defect? Or might it simply reflect the fact that horses are inherently maladapted to dietary starches and sugars?

Similar pathologic findings in people with muscle dysfunction have led to findings of underlying enzyme defects. In people with glycogen storage myopathies similar to EPSSM, a wide range of clinical signs is possible: these include ER, exercise-induced painful or non-painful muscle spasms, progressive muscle atrophy, and weakness [23]. Different clinical manifestations of muscle dysfunction often occur within human families with the same genetic defect. There are several human metabolic myopathies involving abnormalities of enzymes involved in carbohydrate metabolism [23]). Curiously, years of research and thousands of research dollars later, no defects in glycolysis or glycogenolysis can be found in the affected horses [12, 24]. It would appear that the equine disorder is somewhat unique.

It is generally agreed that EPSSM is an inherited disorder. The mode of inheritance, however, is still controversial. Valberg suggests autosomal recessive inheritance of this trait in Quarter horses, based on visual examination of pedigrees. This study included three cases of EPSSM in QH/Arabian and QH/TB horses [25], which is puzzling, since autosomal recessive traits are not typically manifested in crossbreds. Fifty percent (50%) of Warmbloods biopsied were diagnosed with EPSSM [26]. This included a wide variety of breeds such as Dutch Warmblood, Hanoverian, Westfalian, Canadian Warmblood, Irish Sport Horse, Gerdlander, Hussien, and Rheinlander. No reports on the potential inheritance of EPSSM in Warmbloods have been published, and little is known about this form of EPSSM, because no biochemical or physiological studies have been performed in Warmbloods with EPSSM.

The high incidence of EPSSM in Draft breeds and the occurrence in a Belgian mule [27] suggests that a form of dominant inheritance is also possible. Initial examination of pedigrees from registered Belgians with EPSSM suggested that most Belgians, at least in North America, trace back to a small number of foundation lines. This is not surprising given the relatively few purebred Draft horses left for breeding following the Great Depression and the Industrial Revolution in the United States. If the data regarding incidence of EPSSM in Draft-related breeds are even close to accurate (45-86%), it would appear that trying to breed away from this trait in these breeds would be extremely difficult. In fact, there is some suggestion that horses with EPSSM, when they are able to deal with the condition, are superior in temperament, conformation, and even more importantly, performance. In Quarter horses this trait has been linked to lineage from popular performance stallions. If so, it may be that we have actually somehow selected for this type of metabolism.

That a metabolic disorder could affect so many breeds of horses and ponies may be difficult to comprehend. Consideration of the origins of modern horse and pony breeds may help to resolve this issue. For example, the American Quarter Horse is descended from several different breeds and the dam of one foundation Quarter horse stallion was one-half registered Percheron [28]. Given that EPSSM has been described in Arabian horses [15], and that Arabian bloodlines can be found in virtually all modern horses and pony breeds if one looks back far enough, the wide range of breeds affected becomes less surprising. The fact that these are high performing horses makes this condition very different from hyperkalemic periodic paralysis (HYPP), another myopathy in Quarter horse-related breeds. HYPP is a single-gene defect passed on from a single stallion whose muscle disorder led to development of heavy-musclered halter horses, but whose performance attributes were woefully inadequate [29]. Whereas HYPP is a recently introduced genetic disorder, it is now believed that EPSSM has been around for as long as horses have been recognized to have ER (tying-up, Monday morning disease, azoturia, paralytic hemoglobinuria, post anesthetic myopathy, or shivers - all manifestations of what we now consider to be EPSSM).

Based on the characteristic finding of glycogen-related polysaccharides in muscle from affected horses, the logical conclusion was that there must be something wrong with carbohydrate metabolism in these horses. The focus moved to whole body glucose metabolism and the uptake of blood glucose into muscle cells following a high starch and sugar meal in horses. Since skeletal muscle has a major role in body glucose metabolism [30], there is evidence that EPSSM may involve more rapid uptake of blood glucose into muscle cells [31]. De la Corte reported slightly lower than normal blood insulin responses in EPSSM horses (not on high fat diet) that were associated with a rapid decrease in blood glucose following intravenous glucose injection. This suggested that EPSSM horses may have an increased sensitivity to insulin. Preliminary studies of two Draft-related EPSSM horses following two years of diet change have found normal blood glucose curves following intravenous glucose administration, but these horses had abnormally prolonged insulin curves with a delayed insulin peak. The findings of these very preliminary studies suggest that a high fat and low starch and sugar diet may induce a degree of insulin resistance in EPSSM horses. Curiously, this effect was not apparent in the control horse on the same high fat and low starch and sugar diet for the same period, in which the insulin curve was virtually identical to that previously reported following IV glucose administration to normal horses on a low fat diet [32].

It is not surprising that both groups working on this problem (the PSSM group and EPSM group) independently began testing the effects of a diet with reduced starches and sugars and added fat as an alternative energy source. It very quickly becomes clear that this sort of diet is exactly what these horses needed. Some EPSSM horses improve following elimination of all grains from the diet and addition of as little as 0.5-1.0 kg of a 20% rice bran fat supplement [33]. Careful analysis of dietary nutrients and following a prescribed diet in over 250 affected horses indicates that diets that are very high in fat, high in fiber and low in starch and sugar are the most successful. Diets that contain at least 20% of total daily calories from fat, which equates to about 0.45 kg fat per 450 kg of horse per day, added to feeds that are less than about 33% starch and sugar by volume, are recommended [14].

Successful EPSSM diets can include either grass or alfalfa hay [13, 14]. Many higher fat and fiber feeds are being developed for horses, but to date all still require some additional vegetable oil or additional 100% fat source to achieve the proper ratio of calories. For many horses, addition of about 480 ml of vegetable-based oil to a forage-based feed has proven to be the most economical, feasible, and effective type of diet. Regular exercise, even if it is just turnout, is also important. It takes about four months for full fat adaptation in these horses [11, 13, 14], although transient improvement may be seen within the first few weeks of diet change. Improvement is a good indication that the therapy will be successful, even if there is still evidence of muscle dysfunction at some time during the first 4 months [13, 14]. Other positive changes, including improved attitude, muscling, exercise tolerance, way of going, and alleviation of back pain have also been reported in many horses after diet change. Dietary therapy also resulted in a significant decrease in post exercise serum CK and AST levels in EPSSM horses [6, 12, 13], indicative of reduced exercise-induced muscle injury.

Whether dietary therapy results in decreased storage of muscle glycogen in EPSSM horses is controversial. Research has had mixed responses. What has been surprising is that repeated evaluation of muscle biopsy samples from a small number of EPSSM horses, following years of diet change that has resulted in complete control of clinical signs, has found that, subjectively, there is no change in the number of polysaccharide inclusions (Valentine, unpublished data). This finding, and the report by De La Corte [34] of evidence of muscle damage in EPSSM weanlings prior to recognition of amylase-resistant inclusions in myofibers, suggests that the abnormal glycogen and complex polysaccharide storage in horses with EPSSM reflects an underlying metabolic abnormality and that the inclusions are not the primary cause of the muscle dysfunction. More controversy!

Owners of horses with EPSSM should seriously consider whether such horses should be used as breeding animals. Horses that manifest severe disease from an early age, or horses that do not respond well to dietary therapy, risk passing a severe form of this disorder on to their offspring [25]. However, given the high incidence of EPSSM within certain breeds and the apparent performance capabilities of EPSSM horses, it may not be feasible or even appropriate to try to breed away from this condition. The ability to control signs of muscle dysfunction with diet change and exercise suggests that EPSSM may best be considered a problem with a genetic component that can often be controlled effectively with proper management.

Very recently, breeding trials of Quarter Horses with EPSSM were conducted. Three independent publications looking at genome information, DNA fragment assays and the genetics of EPSSM families of horses identified the *GYS1* mutation. This dominant mutation accounts for approximately 80% of EPSSM cases in Quarter Horses and related breeds, and is now termed **type-1** EPSSM [35, 36]. The 20% of EPSSM horses that do not possess the *GYS1* mutation most likely have a distinct glycogen storage disease [35, 36], now termed **type-2** EPSSM. In a subset of type-1 EPSSM horses, the clinical severity is modified by a second genetic mutation for **malignant hyperthermia (MH)** [37]. Horses with both the *GYS1* and MH mutation have more severe clinical signs and poorer responses to management strategies. Although the MH mutation is present only in Quarter Horses and Quarter horse-related breeds, the type-1 EPSSM mutation has been found in at least 17 different horse breeds [36], and it is likely to have originated before the formation of the modern breeds known today [35]. Type-2 EPSSM also seems to be found in Warmblood and light breeds other than Quarter Horses. The genetic test for type-1 EPSSM and the modifying gene MH are now commercially available at the University of Minnesota Diagnostic Laboratory. Diagnosis of type-2 EPSSM will require examination of a muscle biopsy until the genetic basis for this disorder is fully identified.

It is possible that horses are being diagnosed with EPSSM and put on dietary therapy when in fact they do not have this disorder. The high fat, high fiber, low starch and sugar diets that have been designed for horses with confirmed or suspected EPSSM are inexpensive and are safe and nutritious for any horse. If, after 4 months of diet change an owner does not see any positive effects of diet change, then the diagnosis of EPSSM may have been incorrect. But, during the time of dietary therapy he or she has not invested a fortune, has not risked side effects of medications, has reduced the risk of colic and of laminitis, and at the end of this time is likely, at the very least, to have a horse with a great shiny hair coat.

Dietary therapy: could it really be that simple? It is hard to believe that a variety of equine problems that have been around for so long really have a simple answer in dietary management.

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