She’s All Tied Up

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Introduction

Polysaccharide Storage Myopathy (PSSM) is a disorder of equine skeletal muscle that is characterized by excessive accumulations of indigestible, abnormal glycogen within skeletal muscle fibers.[1] PSSM is one of the many disease processes that is associated with the syndrome of exertional rhabdomyolysis (ER). This syndrome includes diseases that cause muscle pain and cramping associated with exercise and ensuing increases in serum muscle enzymes.[3] Previously termed “Monday Morning Disease”, exertional rhabdomyolysis has plagued horses for over a century and has many names, including “tying up” and “azoturia”.[4] Exertional rhabdomyolysis has several specific disease entities that cause a collection of similar clinical signs associated with muscle pain.[4] This case focuses on one cause of ER, polysaccharide storage myopathy.

History and Presentation

A 15 year old Quarter Horse mare presented to MSU-CVM’s Equine Department on March 4th, 2019 for evaluation of a stiff gait in the hind end and re-evaluation of previously diagnosed hock joint arthritis. She was diagnosed with arthritis of both distal tarsal joints via radiographs by her referring veterinarian in 2018. The mare was a pleasure horse used for trail riding. Her owner recently noted that she had a very stiff, choppy gait which would worsen after a long ride. She was also noted to “tie up” and have muscle fasciculations over her hind end when she got tired. The mare had been previously tested for the genetic mutation causing hyperkalemic periodic paralysis (HYPP) and was determined to be NN, meaning that she was not a carrier of the gene.

On presentation, the mare was bright, alert, and responsive, weighing 585 kilograms with a body condition score of 6 out of 9. Her vital parameters included a mildly elevated temperature of 101.2 degrees Fahrenheit, a normal pulse of 32 beats per minute, and an elevated respiratory

rate of 36 breaths per minute. Her capillary refill time was less than 2 seconds and her mucous membranes were pink and moist. Cardiothoracic auscultation revealed normal bronchovesicular sounds and no heart murmurs were noted. Normal borborygmus was heard in all four abdominal quadrants.

Diagnostic Approach

A baseline serum biochemistry profile was collected and revealed a mildly increased creatine kinase (CK) with all other values within normal limits. To begin the lameness examination, a motion assessment was performed at the walk and trot, both in a straight line and in circles to the left and right. While moving in a straight line, a shortened stride was observed in her hind end with a slapping motion at the end of the swing phase of the trot, similar to a horse with fibrotic myopathy. A slight but inconsistent head nod was also noted. Next, to further determine the source of the head nod, she was trotted in circles to the left and right—an enhanced head nod was noted when circling to the right and a slight head nod was also seen when circling to the left. After palpating the muscles of her hindquarters, it was observed that there was clear muscle definition and palpable thickening at the insertion of the semitendinosus muscle.

Second, flexion tests were performed on both hindlimbs in attempt to localize any hindlimb lameness. She demonstrated an increased lameness on all three flexions of the left hind (strong positive with distal limb flexion and mild positive with the stifle and upper limb flexion) and a mild increase in lameness on the upper limb flexion of the right hind limb.

At this time, the mare was seen coughing and sweating more than expected for her activity level. Due to these observations and her slightly increased temperature on presentation, a rebreathing bag examination was performed to better assess her lungs. It was determined that all

lung fields sounded normal and the rebreathing exam was within normal limits. Her temperature was taken again and was 101.6 degrees Fahrenheit.

After completion of a thorough lameness evaluation, it was determined that there were several sources of lameness. Both forelimbs were affected, with a mild 3/5 lameness of the right and a mild 2/5 on the left. Both hindlimbs were also affected, with a 3/5 lameness noted bilaterally. This was determined to be due to a mechanical lameness, specifically fibrotic myopathy. The resulting gait is known as a "goose-stepping" gait and is commonly seen in horses with fibrotic myopathy—the foot jerks onto the ground as the horse tries to step forward.[5] Although this can explain why the mare was observed to have a stiff gait, no muscle fasciculations or other signs of the described tying up were seen. In order to assess her muscle function and determine if she was, in fact, having episodes of tying up or rhabdomyolysis, an exercise trial was the next step.

In order to perform this test, the patient would be exercised at a canter for 10 minutes and the pre-exercise bloodwork drawn earlier in the day would be compared with bloodwork drawn four hours post-exercise. The main value of interest was the creatine kinase, which is an indicator of muscle cell damage. The mare was taken to the round pen to initiate the exercise trial. She was extremely reluctant to move forward, and it was difficult to keep her moving forward in a trot. At the five-minute mark, she was profusely sweating and small muscle fasciculations were seen all over her body. At this point, it was decided to discontinue the exercise trial due to signs of rhabdomyolysis. Her temperature was taken at this time and had risen to 102.7 degrees F. Walking back into the clinic, her gait became extremely choppy and stiff, and she was reluctant to move. An iSTAT was performed to assess her electrolytes and ensure she was not having an HYPP attack; although she was previously tested and negative for

this genetic mutation, the signs were consistent with an episode of hyperkalemic periodic paralysis. However, her sodium and potassium were within normal limits so this was ruled out. A blood sample was collected four hours after exercising and submitted for assessment of creatine kinase levels.

Pathophysiology

Polysaccharide storage myopathy is an inherited metabolic glycogenosis that is characterized by the presence of high muscle glycogen concentrations along with the presence of amylase resistant aggregates of abnormal glycogen in muscle fibers of affected horses.[3] After extensive, retrospective genetic testing and research, it was determined that the majority of cases of horses that were previously diagnosed with PSSM via muscle biopsy all had the same genetic mutation.[2] This mutation was determined to be an autosomal dominant gain of function mutation of the glycogen synthase 1 (GYS1) gene on codon 309 and was consistently associated with the presence of the abnormal, amylase resistant glycogen in equine skeletal muscle.[2,6] However, there were some cases of horses with all of the clinical and histologic signs of PSSM that did not possess this genetic mutation.[3] Therefore, PSSM was divided into two categories: PSSM-1 and PSSM-2. The form of PSSM that is associated with the GYS1 H309G mutation is now called polysaccharide storage myopathy type 1; the form that that does not have this specific mutation but has a yet unknown genetic linkage is termed polysaccharide storage myopathy type 2. [3,6] For the purposes of this case and paper, PSSM-1 will be the focus of discussion.

The genetic mutation that causes this disease has been found in over 20 different horse breeds; however, in North America, it is most frequently seen in draft breeds that originated from continental Europe and in Quarter Horse related breeds.[7] This genetic mutation is very uncommon in most light breeds, including Thoroughbreds, Arabians, and Saddlebreds.[3] The

estimated prevalence in Quarter Horses ranges from six to ten percent of the breed possessing this mutation, with halter-bred Quarter Horses being more predisposed, with an estimated 28 percent prevalence.[3] Although many of the horses that possess the GYS1 mutation regularly display clinical signs, there are many factors that affect the severity of their presentation—a horses' diet, activity level, and environment all play a role.[3] Affected horses usually begin displaying signs around six years of age, although it can be seen in foals and weanlings as well.[2] Both sexes are affected equally, but horses that are unfit or have been in a period of rest prior to training, as well as horses that consume a large amount of non-structural carbohydrates, are at the highest risk for development of clinical signs.[2]

The clinical syndrome seen with polysaccharide storage myopathy is caused by the presence of the glycogen synthase 1 genetic mutation.[8] Glycogen synthase (GS) is an enzyme that produces glycogen when influenced by the presence of insulin and glucose-6-phosphate (G-6-P).[1] When the GYS1 mutation is present, it results in overactivity of this enzyme, both in normal situations, and when under the influence of G-6-P.[1,2] This results in GS that is constitutively active, leading to the classic histologic findings of PSSM-1: excessive intracellular glycogen and the presence of amylase resistant glycogen aggregates.[9] The abnormal glycogen that is resistant to digestion by amylase is produced due to an imbalance in the ratio of glycogen synthase to glycogen branching enzyme (GBE), an enzyme that is responsible for forming bonds that make branches in the glycogen molecules.[9] The continuously high activity of GS, along with the normal activity level of GBE, which is not affected by the genetic mutation, leads to the production of large, less branched glycogen molecules that are not easily digested by amylase.[2,9] This increased concentration of glycogen in muscle fibers leads to cellular metabolic issues, as

the breakdown and digestion of glycogen cannot occur while glycogen is being produced constantly, as it is in PSSM horses.[10]

The overall result is an energy deficit in the muscle cell and reduced energy availability within the affected muscle fibers.[1,10] When looking at these muscle cells on an ultrastructural level, it was observed that the abnormal glycogen that was accumulated inside cells displaced or reduced the number of mitochondria and myofibrils.[12] This resulted in decreased number and abnormal structure of mitochondria in affected cells, leading to an overall reduction in mitochondrial activity.[12] Genes in the affected cells were also evaluated and several specific genes were altered (either up-regulated or down-regulated) which resulted in changes in protein synthesis, apoptosis, cellular movement, and proliferation—signs of mitochondrial degeneration and dysfunction.[10,12] PSSM affected muscle cells were also found to display signs of severe, chronic inflammation and hypoxia.[12] These specific changes in cellular and mitochondrial function along with the impaired energy transformation and metabolism inside cells are what lead to the clinical syndrome of PSSM, although research is still ongoing to prove the exact mechanism.[10, 12]

Quarter Horses that are affected with PSSM can display a wide array of clinical signs, dependent upon if the disease is acute or chronic. Acute attacks include muscle stiffness, sweating, reluctance to move forward, firm muscle contractures, and muscle fasciculations, most commonly in the flank area.[2,3] Chronic signs of the disease include an overall lack of energy, reluctance to work or move forward, exercise intolerance, poor overall performance, undiagnosed lameness, generalized pelvic limb stiffness, and repeated episodes of rhabdomyolysis.[1,3] It has been determined that horses that are out of shape or are consuming a diet mostly made up of non-structural carbohydrates are more prone to having episodes of

muscle pain or rhabdomyolysis.[2] When a horse with the GYS1 mutation consumes a high amount of starch, the muscle lactate and citrate concentrations rise while the glucose-6-phospahte levels decrease which led researchers to believe that the enhanced activity of GS may impair oxidative metabolism of substrates like pyruvate or fatty acids in the cell.[2] The overall reduction in oxidative metabolism could be the cause of the cell's inability to properly fuel muscle contraction during exercise.[2] Due to this, one of the cornerstones of treatment is a diet change, which will be discussed in further detail in a later section.

Treatment and Management

Evaluation of all clinical signs, along with the mare's history and signalment, led to the presumptive diagnosis of PSSM. Upon return to the clinic after her exercise trial, she was slowly hand walked until the overt muscle fasciculations ended and was then administered one dose of Flunixin Meglumine intravenously to help with pain and inflammation associated with rhabdomyolysis. Four hours after the exercise trial, a blood sample was collected and submitted for analysis of creatine kinase levels, where a three- to four-fold increase from basal CK activity is indicative of exertional rhabdomyolysis, and normal horses will show minimal change in CK with a submaximal exercise test.[4] A three- to five-fold increase in serum CK is indicative of necrosis of twenty grams of normal muscle tissue.[11] The mare was discharged with the presumed diagnosis of PSSM with instructions for instituting a diet change and new exercise regimen. When the blood test results were returned, this diagnosis was supported further, with her serum CK rising from 306 U/L to 20,500 U/L, a nearly 67-fold increase.

Although there is no cure for this genetic myopathy, it has been shown that a change in diet as well as exercise routine can greatly improve clinical signs. If a horse with PSSM is fed a diet that is high in fat and low in starch and sugar, the overall glucose levels will be decreased,

thus leading to lower glucose uptake into muscle cells.[2] This means that less glycogen will be synthesized and therefore, there will be less glycogen present in muscle cells.[2] This change, along with a regular exercise regimen, shows a beneficial response in about 70 percent of horses, with many able to return to performance levels.[2,3] Regular daily exercise was shown to be of more benefit than a horse being confined to a stall, with the changes in CK levels being less profound in the horses that were able to work daily.[3] Intensity of exercise was proved to be less important than duration and consistency—regular, daily exercise is the key to reduce muscle damage.[2,3]

Case Outcome

The mare was discharged with the presumptive diagnosis of polysaccharide storage myopathy due to her signalment, history, and clinical signs. Care instructions included information about altering her diet and transitioning to a feed that was low in non-structural carbohydrates along with information about a new exercise and turn out regimen. The prognosis for this disease is good for return to function with adherence to the diet and exercise protocol, although these horses will be more likely to have problems with chronic muscle soreness than non-PSSM horses.[3] However, more than 75% of these horses will no longer have clinical episodes of tying up with strict adherence to a diet and exercise regimen.[8] At the time of this report, the mare's owner reports that she has done very well since discharge and adjusted well to a commercial equine diet that is low in starch and high in fat. She lives on pasture and has plenty of room to run, roam and eat Bermuda grass daily. Her owner continues to take her on trail rides and she has had no more episodes of rhabdomyolysis since beginning the new diet. Overall, she is doing very well at home with the suggested adjustments to her lifestyle.

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