HERITABLE DISEASES OF THE AMERICAN QUARTER HORSE AND THEIR MANAGEMENT

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The recent development of equine genome maps and the complete sequencing of the horse genome have increased the pace of genetic discovery resulting in the identification of several genetic diseases in the Quarter Horse. The first genetic disease was identified in 1992 and was a mutation in the sodium channel gene, SCN4A that is responsible for potassium-induced paralysis known as HYPP (Rudolph *et al*., 1992). Glycogen branching enzyme deficiency, a metabolic genetic disease that is fatal in the fetus and neonate was identified and determined to be caused by a mutation in the GBE1 Gene (Ward *et al*., 2004). A mutation in peptidyl-prolylisomerase B was found to be associated with hereditary equine regional dermal asthenia (HERDA), a progressive skin disease that typically develops between 6 months and 2 years of age (Tryon *et al*., 2007). Polysaccharide storage myopathy (PSSM), responsible for chronic exertional rhabdomyolysis, is caused by a mutation in glycogen synthase 1 (McCue *et al*., 2008). In addition, malignant hyperthermia has been identified in Quarter Horses and occurs in exon 46 of the skeletal muscle ryanodine receptor gene (RyR1) (Alelman *et al*., 2008).

Glycogen branching enzyme deficiency (GBED) is an autosomal recessive glycogen storage disorder that affects Quarter Horse or Paint Horse neonates or aborted fetuses. The mutation in the GBE1 gene markedly reduces the function of the glycogen branching enzyme. As a result, tissues such as cardiac, skeletal muscle, liver and the brain cannot store and mobilize glycogen in order to maintain normal glucoses homeostasis. Carriers of GBED trace back to the sire King P234 in most cases, although King's sire Zantanon may have also carried GBED. Currently, the carrier frequency in the Quarter Horse breed is estimated at 8.3% and 7.1% in the Paint Horse breed (Wagner *et al*., 2006). Affected foals may be aborted, stillborn or born alive. Those born alive appear weak and may progress to sudden death following hypo-glycemic seizures. All foals studied to date have died by 18 weeks of age due to severe muscle weakness (Valberg and Mickelson, 2006). Glycogen is a required energy source in the rapidly growing fetus and neonate. Tissues from GBED foals have no measureable GBE-enzyme activity or immuno-detectable GBE and cannot form normally branched glycogen. Aborted fetuses or foals of Quarter Horse-related breeds that die at less than 8 weeks of age should have cardiac and muscle sections obtained for periodic acid-Schiff (PAS) staining. Abnormal polysaccharide can be identified in neural tissue and is consistently found in the liver. However, the most accurate diagnosis of GBED is obtained through genetic testing by licensed laboratories such as the University of California-Davis (www.vgl.ucdavis.edu) or Vet Gen (www.vetgen.com). Mane or tail hairs with roots intact should be submitted.

Malignant hyperthermia is an autosomal dominant mutation that has been identified in Quarter Horses that developed marked hyperthermia and metabolic acidosis during inhalation anesthesia. The prevalence of the RYR1 mutation is not known and is not associated with recurrent exertional rhabdomyolysis. Classic episodes of malignant hyperthermia are diagnosed based on clinical signs of lactic acidosis and hyperthermia (> 40° C) under halothane anesthesia or following succinylcholine injection. A PCR based genetic test is now available. In a horse suspected to have malignant hyperthermia, pretreatment with oral dantrolene (4 mg/kg) 30-60 minutes prior to anesthesia would be indicated (Valverde *et al*.,). Other means to address hyperthermia would include external application of alcohol, fans, chilled intravenous fluids with sodium bicarbonate and mechanical ventilation, although treatment options are usually unsuccessful once the episode is underway. Genetic testing for this condition is available at the University of California-Davis (www.vgl.ucdavis.edu) and the University of Minnesota (www.vdl.umn.edu/vdl/ourservides/neuromuscular.html).

Hereditary equine regional dermal asthenia (HERDA), also known as hyperelastosis cutis, is an autosomal recessive trait affecting horses of Quarter horse lineage. The genetic defect is a G to A substitution at codon 115 in equine cyclophilin B (PPIB) (Tryon *et al*., 2007).The condition is characterized by loose, hyper-extensible and fragile skin. The gene has been estimated to occur in 3.5% of Quarter Horses in general, but in 28% of elite cutting horses (Tryon *et al*., 2005). Clinical signs usually do not occur until 1.5 years of age, on average, when training begins. Affected horses present with seromas, hematomas, open wounds and sloughing skin. Affected areas are primarily located along the dorsum due to saddle trauma but can occur in other parts of the body. Treatment of lesions is supportive in nature although keeping affected horses out of direct sunlight has been shown to be effective in slowing the progression of lesions. A genetic test to screen for the mutation is available through the University of California and Cornell University.

Polysaccharide Storage Myopathy (PSSM) was first identified in 1992 and is a common form of tying-up in many horse breeds including Quarter Horses, American Paint Horses, Appaloosas, Warmbloods and draft breeds. The condition is characterized by excessive and abnormal storage of sugar (polysaccharide) in muscle cells. The condition is due to an autosomal dominant point mutation in the glycogen synthase 1 gene (GYS1) which appears to cause unregulated synthesis of glycogen. When all horses screened for the condition at the University of Minnesota Neuromuscular Diagnostic Laboratory by muscle biopsy were screened for the genetic mutation, it became clear there was a subset of horses with PSSM that did not have the GYS1 Mutation. Therefore, the nomenclature for PSSM has changed; type 1 PSSM refers to horses with the GYS1 mutation and type 2 PSSM refers to horses diagnosed with abnormal glycogen storage in muscle biopsy that lack the GYS1 mutation (Valberg and Mickelson, 2007). Clinical signs of the condition include muscle pain, stiffness, sweating, exercise intolerance, weakness and reluctance to move with the hindquarters most frequently affected. A definitive diagnosis can be made by muscle biopsy for both type 1 and 2 PSSM or genetic testing for type 1 PSSM at the University of Minnesota Veterinary Diagnostic Laboratory (www.vdl.umn.edu/vdl/ourservices/neuromuscular.html). Whole blood or hair including the roots should be submitted. Treatment for an acute episode includes stall rest for no more than 48 hours, assessment of hydration status and rehydration if indicated to prevent kidney damage, sedatives, and anti-inflammatories. Prolonged stall confinement may result in an increased incidence of PSSM and therefore, affected horses should have access to turnout as soon as possible. An appropriate exercise regimen following an episode of rhabdomyolysis would be a 2 week period of turn out while the diet is being changed and then a gradual return to exercise, with successive addition of 2 minute intervals of walk and trot beginning with only 4 minutes of exercise and working up to 30 minutes after 3 weeks. The objective of increasing the duration of exercise is to augment the capacity of the muscle to oxidize fat and glycogen as energy substrates. Dietary management should be aimed at providing adequate, but not excessive calories by decreasing the glucose load and providing fat as an alternative energy source. Decreasing the dietary starch and sugar (NSC) to <10% of daily digestible energy and increasing dietary fat up to 13% of daily digestible energy combined with a vitamin mineral supplement is recommended (Ribeiro *et al*., 2004). Some commercial feeds meet the recommended nutritional needs of PSSM horses in a single pelleted ration. These feeds typically contain 10 to 15% fat by weight and less than 20% starch or nonstructural carbohydrate by weight.

Hyperkalemic periodic paralysis (HYPP) is an autosomal dominant trait affecting Quarter Horses, American Paint Horses, Appaloosas and Quarter Horse crossbreds. The genetic condition traces back to the Quarter Horse sire Impressive and affects approximately 4% of the Quarter Horse breed (Finno *et al*., 2008). Horses affected by HYPP have been preferentially selected as breeding and show stock due to their phenotype expression of well-developed musculature and results in halter classes. In 1996 the American Quarter Horse Association (AQHA) recognized HYPP as a genetic defect and mandatory testing was instituted with the results recorded on the registration papers for all foals that are descendents

of Impressive and were born after January 1, 1998. In 2007 AQHA ruled that foals born in 2007 or later and that tested homozygous affected for HYPP (H/H) would not be eligible for registration. Horses that tested heterozygous affected for HYPP are designated as N/H and normal unaffected horses are N/N. HYPP is due to a missense mutation (C to G substitution) resulting in a phenylalanine/leucine substitution in the alpha-subunit of the voltage-dependent skeletal muscle sodium channel alpha-subunit (SCN4A). In HYPP horses, the resting membrane potential is closer to firing than in normal horses. Sodium channels are normally briefly activated during the initial phase of the muscle-action potential. HYPP results in a failure of a subpopulation of sodium channels to inactivate when serum-potassium concentrations are increased. The result is an excessive influx of sodium and outward flux of potassium, resulting in persistent depolarization of muscles cells followed by temporary weakness. Clinical signs of HYPP affected horses vary from asymptomatic to daily muscle fasciculations and weakness resulting in recumbency and occasionally, death. Episodes of weakness or paralysis appear similar between N/H and H/H horses. Clinical signs of homozygous HYPP foals include respiratory stridor and periodic obstruction of the upper respiratory tract. Affected homozygous horses also exhibit dysphonia (a high pitched whinny) even between episodes. Foals that are heterozygous (N/H) are less severely affected and typically do not demonstrate clinical signs of disease until they are weaned. In both heterozygous and homozygous HYPP horses clinical signs begin with a brief period of twitching or delayed relaxation of muscles with some horses showing prolapse of the third eyelid. Sweating and muscle fasciculations are usually seen in the flanks, neck and shoulders. During mild attacks, horses remain standing but in more severe attacks the clinical signs may progress to staggering, dog-sitting or recumbency. Episodes last for varying periods of time, but usually last from 15 to 60 minutes. After an episode, horses appear normal. Episodes may be triggered by diets containing > 1.1% potassium in the total daily intake on a dry weight basis. Other precipitating factors include fasting, anesthesia, trailer rides and stress (Spier, 2006). Genetic identification of homozygous and heterozygous HYPP horses can be made by sending mane or tail hair to the Veterinary Genetics Laboratory at the University of California at Davis (www.vgl.ucdavis.edu).

Treatment of horses experiencing episodes includes light exercise when clinical signs are first observed. Feeding grain or corn syrup to stimulate insulin-mediated movement of potassium across cell membranes may also be beneficial. Other treatments include administration of epinephrine (3 mL of 1:1000/500kg IM) and acetazolamide (3 mg/kg every 8-12 h orally). In severe cases, administration of calcium gluconate (0.2-0.4 mL/kg of a 23% solution diluted in 1 L of 5% dextrose) will often provide immediate improvement. An increase in extracellular calcium concentration raises the muscle-membrane threshold potential which attenuates membrane excitability. To reduce serum potassium, IV dextrose (6 mL/kg of a 5% solution) alone or in combination with sodium bicarbonate (1-2 mEq/kg) can be used to enhance intracellular movement of potassium. In most cases, HYPP is a manageable disorder, although severe episodes can be fatal. Decreasing dietary potassium and increasing renal losses of potassium are the primary steps taken to prevent HYPP episodes. Regular exercise is also beneficial. Horses with HYPP can graze most pastures because the high water content of the grass makes it unlikely the horse will consume large amounts of potassium in a short period of time. Horses with HYPP should be fed a balanced ration containing between 0.6% and 1.1% total potassium concentration and meals containing < 33 g of potassium (Reynolds *et al*., 1998). High potassium feeds such as alfalfa hay, orchard grass hay, brome hay, soybean meal, electrolyte supplements, canola oil, kelp-based supplements, sugar molasses and beet molasses should be avoided. Ideally late cuts of Timothy or Bermuda grass hay; grains such as oats, corn, wheat and barley; and beet pulp should be fed in small meals several times a day. The potassium concentration of forages can vary widely, so it may be prudent to perform a forage analysis to determine potassium concentrations before feeding. Commercially available complete feeds with a guaranteed potassium content may be more convenient for some HYPP horses. HYPP horses should be fed several times a day and allowed frequent access to a large paddock or pasture. Several drugs have been used for prevention of clinical signs. Acetazolamide (2-4 mg/kg orally, every 8-12 hours) or hydrochlorthiazide (0.5-1 mg/kg orally, every 12 hours) have both been used with success. These agents

exert their effects through different mechanisms; however, both cause increased renal potassium ATPase activity. Acetazolamide has been shown to stabilize blood glucose and potassium by stimulating insulin secretion. Since HYPP is a dominant trait, breeding a heterozygous affected horse (N/H) to a normal horse (N/N) results in a 50% chance of producing a foal heterozygous for HYPP, while breeding a homozygous affected horse (H/H) to a normal horse (N/N) results in a 100% chance of producing a heterozygous affected horse (N/H). Owners of affected horse should advise their veterinarian of the horse's HYPP status before anesthesia or procedures requiring heavy sedation. Horse descended from Impressive should be tested for HYPP during any pre-purchase examination.

References

Alelman, M., J. Riehl, B. Aldridge, R.A. Lecouteur, J.L. Stott, and I.N. Pessah. 2004. Association of a mutation in the ryanodine receptor 1 gene with equine malignant hyperthermia. Muscle Nerve 30:356-365.

Bowling, A., G. Byrns, and S. Spier. 1997. Evidence for a single pedigree source of the hyperkalemic periodic paralysis susceptibility gene in quarter horses. Animal Genetics 27:279-281.

Finno, C., S.J. Spier, and S.J. Valberg. 2008. Equine diseases caused by known genetic mutations. Vet. J. doi:10.1016/j.tvjl.2008.03.016.

McCue, M., S. Valberg, M. Miller, C. Wade, S. DiMauro, H.O. Akman, and J.R. Mickelson. 2008. Glycogen synthase (GYS1) mutation causes a novel skeletal muscle glycogenosis. Genomics 91:458-466.

Ribeiro, W., S. Valberg, J. Pagan, and B.E. Gustavsson. 2004. The effect of varying dietary starch and fat content on serum creatine kinase activity and substrate availability in equine polysaccharide storage myopathy. J. Vet. Int. Med. 18:887-894.

Reynolds, J., G. Potter, L. Green, G. Wu, G.K. Carter, M.T. Martin, T.V. Peterson, M. Murray-Gerzik, G. Moss, and R.S. Erkert. 1998. Genetic-diet interactions in the hyperkalemic periodic paralysis syndrome in Quarter horses fed varying amounts of potassium: III. The relationship between plasma potassium concentration and HYPP symptoms. J. Eq. Vet. Sci. 18:731-735.

Rudolph, J., S. Spier, G. Byrns, C.V. Rojas, D. Bernoco, and E.P. Hoffman. 1992. Periodic paralysis in quarter horses: A sodium channel mutation disseminated by selective breeding. Nat. Genet. 2:144-147.

Spier, S. 2006. Hyperkalemic periodic paralysis: 14 years later. 2006. Pages 1-5. In: Proceedings of the 52nd Annual American Association of Equine Practitioners Convention.

Tryon, R., S. White, and D. Bannasch. 2007. Homozygosity mapping approach identifies a missense mutation in equine cyclophilin B (PPIB) associated with HERDA in the American Quarter Horse. Genomics 90:93-102.

Tyron, R., S. White, T. Famula, P.C. Schultheiss, D.W. Hamar, and D.L. Bannasch. 2005. Inheritance of hereditary equine regional dermal asthenia in Quarter Horses. Amer. J. Vet. Res. 66:437-442.

Valberg, S., and J. Mickelson. 2007. The interplay of genetics, exercise, and nutrition in polysaccharide storage myopathy. Pages 163-165. In: Proceedings of the 25th Annual American College of Veterinary Internal Medicine Conference.

Valberg, S., and J. Mickelson. 2006. Glycogen branching enzyme deficiency. Pages 351-353. In: Proceedings of the 52nd Annual American Association of Equine Practitioners.

Valverde, A., C. Boyd, D. Dyson, and P.J. Pascoe. 1990. Prophylactic use of dantrolene associated with prolonged post-anesthetic recumbency in a horse. JAVMA 197:1051-1053.

Wagner, M., S. Balberg, E. Ames, M.M. Bauer, J.A. Wiseman, M.C.T. Penedo, H. Kinde, B. Abbitt, and J.R. Mickelson. 2006. Allele frequency and likely impact of the glycogen branching enzyme deficiency gene in Quarter Horse and Paint Horse populations. J. Vet. Int. Med. 20:1207-1211.

Ward, T., S. Valberg, D. Adelson, C.A. Abbey, M.M. Binns, and J.R. Mickelson. 2004. Glycogen branching enzyme (GBE1) mutation causing equine glycogen storage disease IV. Mamm. Genome 15:570-577.