THE PATIENTS WITH RHABDOMYOLYSIS: Commonalities between Horses and Humans

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Introduction

• Exertional rhabdomyolysis (ER): the breakdown of muscle causing a release of intercellular material (myoglobin, calcium, potassium) from the damaged muscle cell.
• Horses and humans are comparable since the pathophysiology is similar, both exhibit injury of the muscle cell, displacement of the intercellular material from the damaged muscle, excessive intracellular Ca2+, which then leads to a persistent contraction of the myofibrils.
• The excess intercellular calcium has lead researchers to believe that it may be related to a mutation in the RYR1 gene.
• RYR1 gene: Mutations in this gene results in defects of the skeletal muscle ryanodine receptor and calcium release channels.
• Polysaccharide storage myopathy (PSSM): a disorder in horses noted by atypical glycogen accumulation and ER. The mutation is a single base-pair substitution in the GYS1 gene resulting in a critical change which causes the enzyme to remain being in the active state.
• GYS1 gene: Mutations in this gene results in defects in the process of both glycogen synthesis or breakdown.

Purpose

• The purpose of this paper is to conduct a literature review to ascertain if there is a correlation between the occurrence of the GYS1 gene mutation in both horses and humans on the incidence of exertional rhabdomyolysis, and if yes, does a low glucose diet reduce the severity of ER symptoms?
• The hypothesis posed is that if diagnosed with exertional rhabdomyolysis, both the human and the horse has a GYS1 gene mutation, since this gene mutation causes an increase in the activity of glycogen synthase.

Methods

The data collected for this research has been by a review of previous literature. The George Mason University databases were used to search for studies on cases of ER, PSSM, and malignant hyperthermia (MH) for common knowledge of these topics. The articles used where those pertaining to ER and PSSM, while articles pertaining to MH where disregarded since both PSSM and MH gives detail about the RYR1 gene. All articles discussing animals but horses and humans where discarded since the research did not detail any significant difference between the other animals and horses. The articles most heavily used where those that elaborated on the RYR1 and or GYS1.

Figure 1. Historical data from M. E. McCue et al. shows the serum CK activity contrasted with the percent of target exercise completed. PSSM_N represents horses that were heterozygous for the GYS1 mutation and homozygous normal at the RYR1 locus. PSSM_MH represents horses that are heterozygous for the GYS1 and RYR1 mutations.

Results

A literature review of 30 articles has been narrowed down to four articles pertaining to the GYS1 gene mutation and dietary control of horses.

• Wilberger et al. collected samples from 101 horses participating in an endurance race, and of the 4.0% that showed symptoms of ER, none had a GYS1 or RYR1 mutation.
• M. E. McCue et al. collected samples from 179 horses and their data concluded that horses with mutations in both GYS1 and RYR1 have a more severe clinical phenotype. Also when PSSM_N and PSSM_MH horses were fed a high-fat, low-starch diet and their exercise tolerance and post-exercise CK activity improved significantly (Fig. 1).
• Ribeiro et al. showed that PSSM horses when consuming a 4% daily intake of starch and 13% daily intake of fat had a significantly lower CK response compared to horses which had a daily intake of starch >8% and an equivalent or lower fat content.
• M. E. McCue et al. collected data showing that the GYS1 gene is consistent with the PSSM phenotype, and that the non-GYS1 forms of PSSM need to be elucidated to better understand the development of ER.

Discussion

The results from the literature suggest that:
1. Humans should be tested for a mutation in the GYS1 gene.
2. If the there is a mutation found in the GYS1 gene, then conduct an experiment on humans testing the effect of a low-glucose, high-fat diet to see if there is a reduction in the severity of the ER symptoms.
3. Human muscle biopsies should be analyzed using periodic acid Schiff’s stain to confirm an excess of glycogen in muscle cell.
4. A questionnaire should be used to look at stress levels and diets of humans to develop a new source of comparison to better improve the knowledge of ER.

Conclusion

While there are common genes (RYR1 and GYS1) believed to be responsible for ER in both horses and humans, very little research has been done comparing the occurrence in both. Other factors such as diet and stress levels are focused on much more heavily in horses, while neglected in research done on humans. Adding a questionnaire or survey to the protocol would prove beneficial to help gain a new source of comparison to better improve the knowledge of ER in humans.

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References