Glycogen-Branching Enzyme Deficiency

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Glycogen-branching enzyme deficiency has emerged as an important cause of abortion and neonatal death in Quarter Horse-related breeds. Approximately 8% of Quarter Horses are carriers of the trait, and the homozygous condition is invariably fatal. Genetic testing is now commercially available. Authors' address: Department of Veterinary Population Medicine and Veterinary Biomedical Sciences, College of Veterinary Medicine, University of Minnesota, 1365 Gortner Avenue, St. Paul, MN 55108; e-mail: valbe001@umn.edu (Valberg).

1. Introduction

Glycogen-branching enzyme deficiency (GBED) is a glycogen-storage disorder that recently has been identified in neonatal Quarter Horse foals or aborted fetuses.[1–3] GBED is an autosomal recessive trait in Quarter Horses and Paint Horses. Thoroughbreds have been screened for GBED without finding this genetic mutation. The disease is caused by a nonsense mutation in exon 1 of the glycogen-branching enzyme (GBE) 1 gene that introduces a premature stop codon. In the homozygous state, this mutation markedly reduces the function of the GBE.[2,4] Carriers of GBED trace back to the sire King P234 in most cases; however, King's sire Zantanon may also have carried GBED. It is not possible to use pedigree analysis to diagnose GBED, because the majority of Quarter Horses are descendants of these two stallions. GBED has likely been in the Quarter Horse breed at least since its inception in 1940.

Approximately 8% of both Quarter Horses and Paint Horses are carriers of GBED.[5] GBED was detected in 2–4% of second- and third-trimester abortions submitted to two diagnostic laboratories.[5] Breeding farms with stallions that are carriers of GBED could expect a higher incidence of abortion because of GBED. In addition, published reports indicate that at least 11 foals have been born with GBED.[3,6] The incidence of GBED in neonatal foals is likely much higher than this, because many foals have likely gone undiagnosed.

2. Diagnosis

Muscle-biopsy specimens from foals with GBED often, but do not always, contain basophilic globules and eosinophilic crystalline material in hematoxylin and eosin stains (Fig. 1).[2,5] Period-acid Schiff's stains show decreased normal background staining for glycogen and para-aminosalicylic acid (PAS) positive globular inclusions with, in some cases, additional smaller crystalline inclusions (Fig. 2).[2] At post-mortem examination, globular inclusions are readily apparent in the Purkinje cells of the myocardium, and inclusions may also be found in cardiac myocytes. Abnormal polysaccharide can be identified in neural tissue and is inconsistently found in the liver.[3]

The most accurate diagnosis of GBED can be obtained through genetic testing. The Veterinary Genetics Laboratory at the University of California at Davis (www.vgl.ucdavis.edu) is licensed by the Uni-

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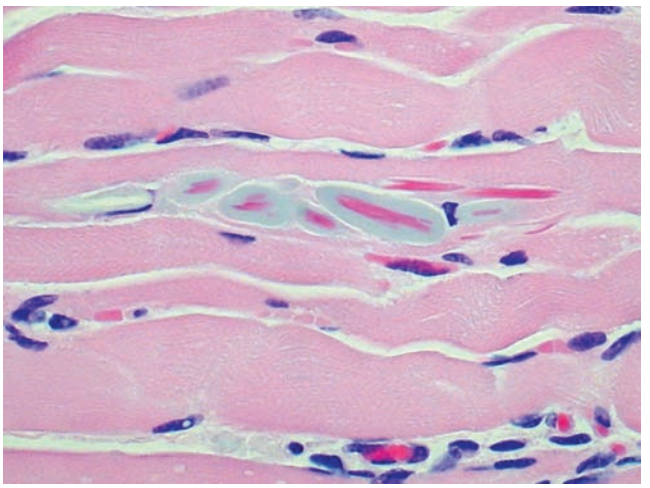

Fig. 1. Globular basophilic inclusions containing eosinophilic material in a skeletal muscle sample from a foal with GBED. Hematoxylin and eosin stain.

versity of Minnesota to test for GBED. Mane or tail hairs with roots intact or fetal liver tissue can be submitted to identify if horses are homozygous or heterozygous for GBED.

3. Clinical Signs

Fetal abortion is a common presentation of GBED.[2,3,6] Foals that survive to parturition are often hypothermic and weak, but they gain strength when given milk by bottle feeding or through assistance to stand and nurse. Correctable flexural deformities of all four limbs are common in GBED foals. Progression of signs can be highly variable. Some foals have early onset of ventilatory failure and die even with mechanical ventilation. Other foals show intermittent collapse because of hypoglycemia, particularly if access to suckling is restricted. Sudden death is reported in some foals, whereas others are euthanized because of muscle weakness and inability to rise.[1,2,6] Most GBED-affected foals die or are euthanized by 8 wk of age; however, one foal survived with nursing care to 18 wk of age.

Common hematological findings in foals with GBED include a low white blood-cell count, often about 4000 cells/μl, as well as moderate elevations in serum creatine kinase (CK), aspartate transaminase (AST), and gama glutamyl transferase (GGT).[2]

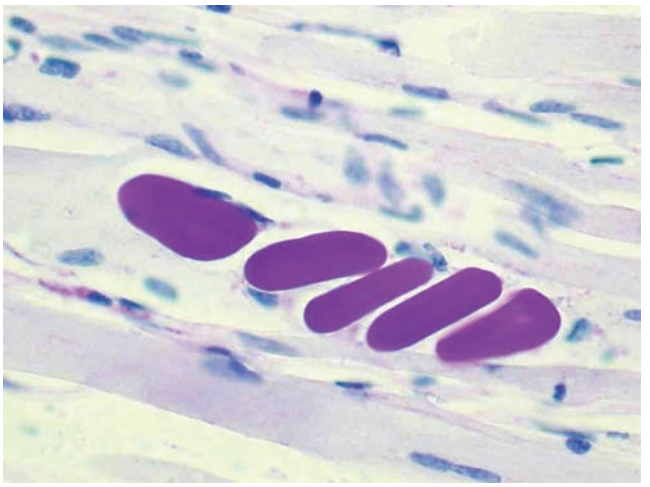

Fig. 2. Periodic-acid Shiff's stain of skeletal muscle from a foal with GBED showing globular PAS positive inclusions within muscle fibers.

4. Pathogenesis

Glycogen is an extremely important energy source for the rapidly growing and developing fetus and neonate. It is synthesized by two enzymes. Glycogen synthase creates straight chains of glucose with alpha 1,4-glycosidic linkages, and GBE creates branches of glucose through alpha 1,6-linkages. Glycogen becomes a compact, highly branched, and energy-dense molecule. Tissues from GBED foals have no measurable GBE-enzyme activity or immuno-detectable GBE and therefore, are unable to form normally branched glycogen.[2] As a result, tissues such as cardiac and skeletal muscle, liver, and the brain cannot store and mobilize glycogen to maintain normal glucose homeostasis. The absence of normally branched glycogen molecules in individuals that possess GBE1 mutations seems to cause a fatal flaw in glucose homeostasis and metabolism in the fetus as well as the newborn foal. This results in muscle weakness, hypoglycemia, seizures, and death. GBED has a similar clinical, biochemical, and molecular basis to glycogen storage disease type IV, which has been described in humans and Norwegian forest cats.[7,8]

5. Treatment

There is no treatment for GBED. Early recognition and euthanasia can save considerable expense for owners of foals in neonatal intensive-care units. It is important that veterinarians and breeders recognize that GBED may present both as foals born alive that subsequently succumb to GBED as well as abortion. Many stallion owners offer a free repeat breeding to owners that lose foals to GBED, and if a diagnosis is not established, the owner will have a 25% chance of having another GBED-affected offspring. Because histologic changes are not always present, PCR analysis for the GBE1 mutation seems to be the most accurate addition to post-mortem diagnostic tests currently used to evaluate aborted fetuses and neonatal foals of Quarter Horse-related breeds.[5]

References

1. Sponseller BT, Valberg SJ, Ward T, et al. Muscular weakness and recumbency in a quarter horse colt due to glycogen branching enzyme deficiency. *Equine Vet Edu* 2003;14:182–188.

2. Valberg SJ, Ward TL, Rush B, et al. Glycogen branching enzyme deficiency in quarter horse foals. *J Vet Int Med* 2001;15:572–580.
3. Render JA, Common RS, Kennedy FA, et al. Amylopectinosis in fetal and neonatal quarter horses. *Vet Pathol* 1999; 36:157–160.
4. Ward TL, Valberg SJ, Lear TL, et al. Genetic mapping of GBE1 and its association with glycogen storage disease IV in American Quarter Horses. *Cytogenet Genome Res* 2003;102: 201–206.
5. Wagner ML, Valberg SJ, Ames EG, et al. Allele frequency and likely impact of the glycogen branching enzyme deficiency gene in quarter horse and paint horse populations. *J Vet Int Med* 2006;(in press).
6. Ward TL, Valberg SJ, Adelson DL, et al. Glycogen branching enzyme (GBE1) mutation causing equine glycogen storage disease IV. *Mamm Genome* 2004;15:570–577.
7. Tsujino S. Glycogen branching enzyme deficiency (Andersen disease). *Ryoikibetsu Shokogun Shirizu* 2001;36:23–24.
8. Fyfe JC, Giger U, Van Winkle TJ, et al. Glycogen storage disease type IV: inherited deficiency of branching enzyme activity in cats. *Pediatr Res* 1992;32:719–725.