Latin Comparative Pathology Group
The Latin Subdivision of the CL Davis Foundation
Diagnostic Exercise

Case #: 11 **Month:** June **Year:** 2011

Answer Sheet

1. Describe the gross abnormalities: Distal colonic contraction with proximal colonic and cecal dilation and meconium retention.

2. Histological findings: Lack of melanin in the skin and absence of myenteric ganglion cells in the affected areas of the colon.

3. Pathological diagnosis: Colonic aganglionosis.

4. Name the condition: Lethal White Foal Syndrome.

5. Most commonly affected breed: Horses with white Overo patterns.

6. Cause: Mutation of the endothelin receptor B (EDNRB) gene (also known as Overo Lethal White Syndrome – OLWS– gene).

Comments:

Overo lethal white syndrome occurs in newborn foals that receive a copy of the mutated OLW gene from each parent. Horses with white Overo patterning are more likely carriers of the gene than solid-colored horses. The mutated gene alters neural crest cell migration or survival, which affects the progenitor cells for melanocytes and intestinal ganglia. Affected foals suffer from aganglionosis of the submucosal and myenteric ganglia of the distal part of the small intestine and of the large intestine, resulting in intestinal immotility and colic. Phenotypically, the altered gene causes lack of skin pigmentation and white coat color. The Overo coat pattern is described as white markings on the lateral and ventral aspects of the neck and torso, whereas a pattern with more white on the dorsal cervical and lumbar

regions and the legs is called tobiano. The Overo coat pattern is seen in the American paint horse, American miniature horse, half-Arabian, Thoroughbred, and crop-out (unregistered because of excessive white marking) quarter horse (QH).

The lethal OLWS gene is an autosomal dominant with variable expression. Heterozygotes demonstrate assorted white coat patterns, and, on very rare occasions, may be solid-colored; for example, if the dominant lethal gene is not being expressed or has spontaneously mutated. Additional studies are necessary to explain the sporadic occurrence of Overo foals from nonspotted QH parents. Two carriers of the mutated gene must be mated to produce a homozygous lethal white foal. According to Mendelian genetics, an Overo × Overo mating would be expected to produce 25% solid-colored foals, and 50% Overo foals, and 25% OLW foals.

Stud book records and observation of born foals show that the probability of producing an OLWS offspring is less than 25%. Possible factors contributing to this unexpectedly low frequency may include failure to report OLW foals to breed registrations, early embryonic loss of homozygote foals, or the relative proportion of carriers in the breeding population.

As there is no treatment for OLWS, testing is essential to prevent its occurrence. Before DNA testing was available, carriers were identified phenotypically by the proportion of white in the coat: the more white, the greater risk of being a carrier. Although this technique identified most carriers, it was inaccurate. A DNA-based test that identifies horses that are heterozygous for the Overo lethal white gene has been developed. The allele-specific polymerase chain reaction test locates and amplifies the specific mutated site in the endothelin receptor B gene (EDNRB gene). This site has been identified in humans with Hirschsprung disease, in whom similar gastrointestinal effects from a mutation of the EDNRB gene are seen.

Proper sampling is important for DNA analysis. Blood or hair samples can be used, but there are difficulties in obtaining DNA from blood, and the blood must be unclotted, kept refrigerated, and delivered to the laboratory within 24 h. Hair samples must include the roots and 15 to 20 hairs, and can be collected from the mane or tail, and require no specific packaging.

Source:

1. Lightbody T. Foal with Overo lethal white syndrome born to a registered quarter horse mare. Can Vet J. 2002 September; 43(9): 715-717

Other References:

1. McCabe L, Griffin LD, Kinzer A, Chandler M, Beckwith JB, McCabe RB. Overo lethal white foal syndrome; equine model of aganglionic megacolon (Hirschsprung disease). Am J Med Genet 1990;36:336-340.

2. Vrotsos PD, Santschi EM, Purdy AK, Mickelson JR. Incidence of an endothelin receptor B mutation in white patterned horses; evidence for genetic heterogeneity in the overo coat pattern. Plant Anim Genome VII Conf, San Diego, California, 1999.

3. Bowling AT. Dominant inheritance of overo spotting in paint horses. J Hered 1994;85:222-225.

4. Yang GC, Croaker D, Zhang AL, Manflick P, Cartmill T, Cass D. A dinucleotide mutation in the endothelin-B receptor gene is associated with lethal white foal syndrome (LWFS); a horse variant of Hirschsprung disease. Human Mol Gene 1998;6:1047-52.

5. James RM, Santschi EM. Role of the endothelin receptor B gene in overo coat color pattern and lethal white foal syndrome. Plant Anim Genome VII Conf, San Diego, California, 1999.

6. Lane PW, Liu HM. Association of megacolon with a new dominant spotting gene (Dom) in the mouse. J Hered 1984;75:435-439.

7. Santschi EM, Purdy AK, Valberg SJ, Vrotsos PD, Kaese H, Mickelson JR. Endothelin receptor B polymorphism associated with lethal white foal syndrome in horses. Mamm Genome 1998; 4:306-309.

Please send your comments/questions to the whole LCPG list by hitting “reply to all”.

A final document containing this material with answers and a brief discussion will be posted on the C. L. Davis website by the end of the current month (http://www.cldavis.org/lcpg_english.html).