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Serum Gamma Glutamyl Transferase Activity in Horses with Right or Left Dorsal Displacements of the Large Colon

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The purpose of this study was to test the hypothesis that horses with right dorsal displacement of the large colon (RDDLC) have elevations in serum gamma glutamyl transferase (GGT) activity when compared with horses with left dorsal displacement of the large colon (LDDLC). Medical records from 37 horses with RDDLC and 48 horses with LDDLC were reviewed. Horses were included for study if the RDDLC or LDDLC was confirmed by exploratory laparotomy or postmortem examination and if a serum GGT measurement was obtained within 24 hours before surgery. The proportion of horses with GGT activity within or above the reference range was determined. Of 37 horses, 18 (49%; exact binomial 95% confidence interval, 32–66%) with RDDLC and, of 48 horses, 1 (2%; 95% CI, 0–11%) with LDDLC had GGT above the reference range. Horses with RDDLC had higher serum GGT than did horses with LDDLC. Of 37 horses, 36 (97%) with RDDLC were discharged with a good prognosis and none returned as a result of hepatic disease. Evaluation of surgical and postmortem examinations revealed that positioning of the colon in horses with RDDLC results in compression of the bile duct, which can cause extrahepatic bile duct obstruction and a subsequent elevation in serum GGT activity.

Key words: Bile duct; Bilirubin; Colic; Hepatic; Obstruction.

Large colon displacement is a common cause of colic in horses and often requires surgical correction. Right dorsal displacement of the large colon (RDDLC) and left dorsal displacement of the large colon (LDDLC) can cause nonstrangulating obstructions, thus preventing the normal flow of ingesta through the bowel lumen without resulting in vascular compromise.[1]

Clinical signs of RDDLC and LDDLC are often similar and characterized initially by variable degrees of abdominal discomfort and distension. Horses frequently respond to symptomatic therapy, but clinical signs recur and the degree of discomfort may be progressive. Hydration and cardiovascular status typically remain normal in the early stages.[1] Diagnosis of LDDLC is primarily accomplished by rectal examination and transabdominal ultrasound examination. It is frequently more difficult to make a definitive diagnosis of a RDDLC than LDDLC because of vague clinical signs and a tendency for variable or nonspecific rectal and ultrasound examination findings.

Elevations in serum activity of hepatic enzyme have been associated with several causes of colic in horses, including cholelithiasis, infectious colitis, large colon displacement, ulcerative duodenitis, proximal enteritis, and neoplasia.[2–9] In this hospital we have observed that horses with RDDLC may have concurrent elevations in the serum activity of the hepatic enzyme gamma glutamyl transferase (GGT) with or without an increase in concentration of conjugated bilirubin. The elevations in GGT return to normal after surgical correction of the displacement.

The purpose of this retrospective study was to test the hypothesis that horses with RDDLC may have elevations in GGT and to determine the occurrence of the observation. Owing to similar presentation, cardiovascular status, and hematologic status, horses with LDDLC served as a comparison group for horses with RDDLC.

Materials and Methods

Horses

Medical records of all horses diagnosed with RDDLC or LDDLC at the Cornell University Hospital for Animals between January 1991 and November 2003 were reviewed. Horses were excluded from the study if they did not have a serum GGT concentration measured within 24 hours before surgery. Horses were also excluded if the diagnosis of RDDLC or LDDLC was not confirmed at surgery or postmortem examination. Horses were grouped according to type of large colon displacement. Horses with LDDLC served as a comparison group for horses with RDDLC.

Data Collection

Data collected for all horses included signalment, history, physical examination findings, rectal examination findings, duration of colic, presence of reflux, CBC and routine serum chemistry results, direct bilirubin concentrations, findings at surgery or postmortem examination, outcome, and liver histopathology.

During the study period laboratory equipment was replaced; therefore, GGT and direct bilirubin values were obtained using 2 different chemistry analyzers with differing reference ranges. The reference range for analyzer 1 was 10–59 U/L, and the reference range for analyzer 2 was 8–33 U/L. Reference ranges for each analyzer were established by testing at least 50 clinically normal horses and using the 2.5 and 97.5 percentiles as the lower and upper limits of the reference range with the middle 95% of the data making up the reference range.

Horses were determined to have GGT and direct bilirubin values within or above the reference range and the proportion of those with high GGT values were evaluated with the exact binomial 95% confidence interval using the algorithm in Epi-Info version 6.04.[a,10] Ninety-five percent confidence intervals that do not overlap indicate that the populations are truly different. This is analogous to a chi-square test for categoric data or a *t*-test for continuous data when the *P* value is $<.05$ but avoids the assumptions needed for using parametric statistics, such as normality of data.

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Table 1. Proportion of horses with elevations in serum gamma glutamyl transferase (GGT) activity, range of GGT concentrations, and median GGT concentrations in horses with right dorsal displacement of the large colon and left dorsal displacement of the large colon. Data are presented according to chemistry analyzer used.

	RDDLC	LDDLC
Total number of horses sampled	37	48
Analyzer 1	10	36
Analyzer 2	27	12
Proportion of horses with elevated serum GGT activity (95% exact binomial confidence interval)		
Total horses sampled	49% (32–66%)	2% (0–11%)
Analyzer 1	50% (19–81%)	3% (0–15%)
Analyzer 2	48% (29–68%)	0% (0–27%)
GGT reference range (U/L)		
Analyzer 1	10–59	10–59
Analyzer 2	8–33	8–33
GGT median (range) in U/L		
Analyzer 1	89 (4–489)	17.5 (9–92)
Analyzer 2	24.5 (7–127)	15.0 (12–20)

RDDLC, right dorsal displacement of the large colon; LDDLC, left dorsal displacement of the large colon; GGT, gamma glutamyl transferase.

The accuracy of using a high GGT value as a screening test for RDDLC in horses with colon displacements was assessed by calculating the sensitivity and specificity. Here, sensitivity is the conditional probability of the GGT being above the reference range in a horse with a colon displacement and was computed as the proportion of horses that had elevations in serum GGT activity of all horses that actually had RDDLC. The specificity is the conditional probability of the GGT being within the reference range in horses with colon displacements and was computed as the proportion of horses that had serum GGT activity within the reference range of all horses that did not have RDDLC. The exact binomial 95% confidence intervals were calculated for the sensitivity and specificity.[10]

Results

Thirty-seven horses with RDDLC and 48 horses with LDDLC fulfilled criteria for inclusion in the study. Horses with RDDLC were more likely to have elevations in GGT than horses with LDDLC (Table 1). A presurgical elevation in GGT activity was identified in 18 of 37 (49%; exact binomial 95% confidence interval, 32–66%) horses with RDDLC and 1 of 48 (2%; 0–11%) horses with LDDLC. GGT activity was unchanged in 2 (18%) and decreased in 9 (82%) of 11 horses with RDDLC in which it was measured postoperatively. A second postoperative measurement of GGT activity was obtained in 3 horses with RDDLC, from 3 to 8 days after surgery, and all were lower than the previous value.

The sensitivity of high serum GGT activity among horses with colon displacements in the diagnosis of RDDLC was 49% (32–66%), and the specificity was 98% (89–100%).

The direct bilirubin concentration was high in 8 of 24 (33%) horses with RDDLC, whereas it was normal in the 2 horses with LDDLC in which it was measured.

All horses had rectal temperatures within the normal range (99.5–101.5°F), and 1 horse had marked (>2 liters) amounts of reflux upon presentation. Evaluation of liver biopsies from 4 horses with RDDLC that had elevations in serum GGT and direct bilirubin concentrations revealed histopathologic evidence of cholangitis or cholangiohepatitis with inflammatory cell infiltration. No bacteria were seen in any of the sections. Of the 48 horses with LDDLC, 4 were euthanized. Postmortem examinations were performed on all 4 horses, and liver lesions were not detected.

Of 37 horses admitted with RDDLC, 36 (97%) survived to discharge. All horses received perioperative antibiotics, but none received long-term antibiotic therapy. All 36 horses were discharged with a good prognosis and none returned as a result of hepatic disease.

Discussion

Horses with RDDLC in this study population had elevations in serum GGT activity when compared with horses with LDDLC. On the basis of the sensitivity of using an elevation in GGT activity in the diagnosis of a RDDLC when compared with LDDLC, the use of GGT as a diagnostic test for a RDDLC would result in many false negatives. However, the presence of high GGT activity in a horse with examination findings consistent with a colon displacement is supportive of RDDLC.

All horses with RDDLC that were evaluated postsurgically had unchanged or decreased GGT activity when compared with admission. Three horses had a third measurement of GGT, and all had values lower than the initial value. The transient nature of increases in GGT and direct bilirubin suggests that the elevations are due to some aspect of the colic episode rather than primary hepatic disease and that correction of the displacement also results in correction of these abnormalities. The slower decline in serum GGT activity as compared with direct bilirubin concentrations after surgery is most likely because GGT and direct bilirubin have different half-lives; because correction of the RDDLC permits immediate normalization of bile flow, whereas biliary inflammation caused by the obstruction requires a longer period of time to resolve; or because of a combination of these 2 reasons.

Few reports exist of horses that have displacement of the large colon and concurrent elevations in GGT with or without increases in direct bilirubin concentration.[5,8] When present, elevations in serum GGT or direct bilirubin concentrations in horses with RDDLC may cause confusion as to the origin of the colic. When colic signs are mild, surgery may be delayed because of concern that the discomfort is a result of primary hepatic disease, causing further colonic edema from longer duration of the displacement before surgical correction, longer duration of medical treatments, and greater expense. Additionally, liver biopsies may be performed unnecessarily because of the concern of primary hepatic disease.

Possibilities for the etiology of the elevation in hepatic enzyme activity in horses with RDDLC include absorption of endotoxin or inflammatory mediators from the intestinal

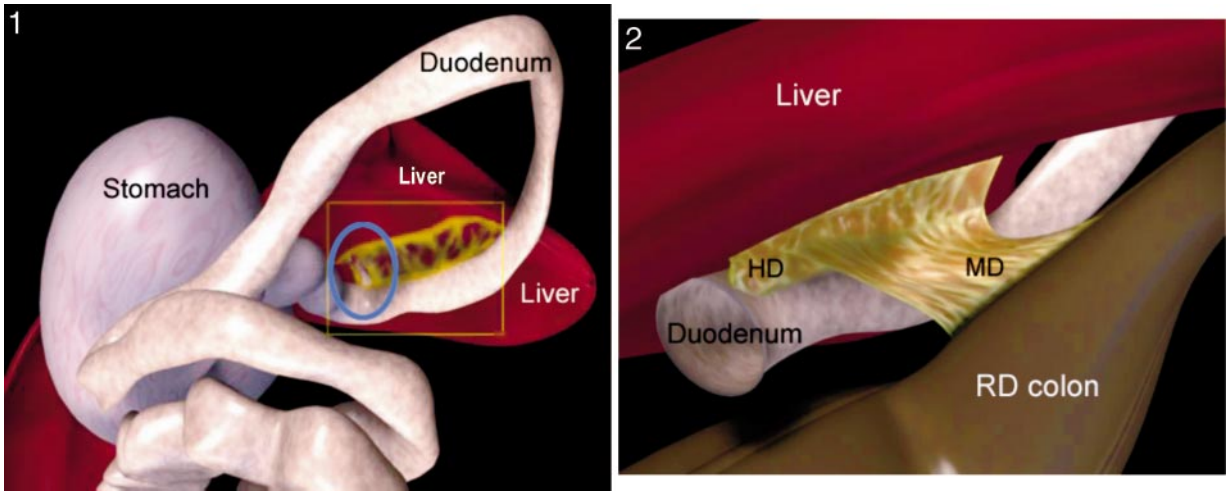

Fig 1. The hepatoduodenal ligament (yellow) attaching the proximal duodenum to the liver. The bile duct (circled in blue) is coursing within the ligament from the liver to duodenum.

Fig 2. The hepatoduodenal ligament and mesoduodenum approaching the liver. RD colon, right dorsal colon; MD, mesoduodenum; HD, hepatoduodenal ligament.

tract into the portal circulation, ascending infection via the common bile duct, or cholestasis secondary to compression of the common bile duct. Absorption of endotoxin or inflammatory mediators is unlikely in horses with RDDLC since signs of inflammation or endotoxemia are typically not present on physical examination or blood work. Hepatic hypoxia is also unlikely because these horses usually do not exhibit marked cardiovascular compromise such as severe tachycardia and dehydration. Evidence of hepatic hypoxia, such as centrilobular necrosis or inflammation, was not present in any liver tissue examined histologically. Ascending biliary infection or regurgitation of small intestinal contents into the common bile duct is more likely to occur in horses with small intestinal distension. Ascending infection by this route is unlikely in horses with RDDLC because they do not commonly have marked gastric reflux or small intestinal distension. If ascending infection occurred because of a generalized ileus secondary to the displacement, similar elevations in GGT, direct bilirubin, or both would be expected in horses with LDDLC. Partial or complete biliary stasis can promote aerobic and anaerobic bacterial growth resulting in evidence of both biliary stasis and bacterial infection on histopathologic evaluation.[11] None of the horses in the study were febrile or were treated with long-term antibiotics and none returned to the hospital because of hepatic dysfunction after discharge, making bacterial overgrowth an unlikely cause of elevations of the GGT, direct bilirubin, or both.

On the basis of evaluation of surgical and postmortem examination, we hypothesize that elevations in GGT with or without elevations in direct bilirubin concentration are due to transient extrahepatic bile duct obstruction, which occurs secondary to the RDDLC. The proximal duodenum is suspended from the right and middle lobes of the liver by the hepatoduodenal ligament. The bile duct travels within the hepatoduodenal ligament for a distance of approximately 5 cm from the portal fissure of the liver to the proximal duodenum (Fig 1). A fibrous sheet of tissue, which is a portion of the mesoduodenum, attaches the right dorsal colon to the visceral surface of the liver. This attachment blends and becomes 1 structure with the hepatoduodenal ligament before its insertion on the liver (Fig 2). When a RDDLC occurs, the right dorsal and ventral portions of the colon are shifted caudally and laterally, placing tension on the short fibrous mesentery. Because of its close association with the hepatoduodenal ligament, tension is similarly placed on this structure. Considerable tension may be placed on these mesenteric structures without markedly changing the luminal diameter of the duodenum. However, the bile duct, within the stretched hepatoduodenal ligament, may become mechanically obstructed causing biliary sludging or stasis and result in an elevation in serum GGT activity. As the process becomes more long standing or tension becomes more severe, obstruction becomes more complete, direct bilirubin is no longer able to be excreted through the bile, and it is absorbed into the bloodstream. The finding of bile duct hyperplasia, as seen on histopathologic evaluation of all biopsies from horses with RDDLC in this study, is suggestive of an obstructive process.[5] Inflammatory cell infiltration was observed but no bacteria were seen, findings often present secondary to cholestasis.[6]

Relief of the biliary obstruction is achieved by surgical correction of the colonic displacement. Normal biliary function is resumed as indicated by the gradual decrease in serum GGT concentrations measured postsurgically. It is likely that a similar biliary obstruction could occur with a large colon volvulus; however, the rapid clinical course of this disease may not allow time for the biochemical changes to be seen.

A study of the anatomy as well as the transient nature of elevations of concentrations in serum GGT, direct bilirubin, or both in horses with surgical correction of RDDLC is supportive of extrahepatic bile duct obstruction secondary to RDDLC. Horses exhibiting abdominal pain with examination findings suggestive of a RDDLC should not have surgery delayed because of elevations in serum GGT or

bilirubin concentration unless historic or ultrasonographic evidence suggestive of primary hepatic disease exists. Horses with high serum GGT or direct bilirubin concentrations secondary to a RDDLC have a good prognosis for recovery and return to normal hepatic function with surgical correction of the displacement and should not require long-term antibiotic therapy to treat the hepatic abnormalities.

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