Secondary hypoparathyroidism attributed to hypomagnesemia in a dog with protein-losing enteropathy

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Severe hypomagnesemia, hypocalcemia, and inappropriately low parathyroid hormone concentrations may develop in dogs with protein-losing enteropathy.

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A 5-year-old castrated male 3-kg (6.6-lb) Shih Tzu was admitted to the North Carolina State University Veterinary Teaching Hospital for treatment of lethargy, profound paresis, and abdominal distention of 2 weeks’ duration. There was an 8-month history of intermittent loose stool associated with eating jerky treats. On physical examination, the dog was underweight with generalized muscle atrophy, moderate sinus tachycardia, pale mucous membranes, mild generalized alopecia and scaling, dependent edema of the ventral aspect of the abdomen, and palpable abdominal effusion. The dog defecated a large volume of malodorous stool during the examination.

Initial biochemical evaluation revealed mild hypoglycemia (73 mg/dl; reference range, 83 to 122 mg/dl), low serum creatinine concentration (0.4 mg/dl; reference range, 0.9 to 1.5 mg/dl), severe hypoalbuminemia (0.8 g/dl; reference range, 2.8 to 3.8 g/dl), hypoglycopenia (1.0 g/dl; reference range, 2.7 to 3.0 g/dl), hypocholesterolemia (81 mg/dl; reference range, 146 to 295 mg/dl), hypocalcemia (ionized calcium concentration, 0.69 mmol/L [reference range, 1.25 to 1.45 mmol/L]; total calcium concentration, 4.2 mg/dl [reference range, 8.8 to 10.7 mg/dl]), hypomagnesemia (0.8 mg/dl; reference range, 1.6 to 2.3 mg/dl), and high alanine transaminase (ALT) activity (338 U/L; reference range, 5 to 35 U/L). Serum parathyroid hormone (PTH) concentration, measured with an assay validated for use in dogs, was within reference limits (9.1 pmol/L; reference range, 2 to 13 pmol/L), and serum 25-hydroxyvitamin D (25OHD) concentration was low (12 nmol/L; reference range, 82 to 285 nmol/L). The serum PTH concentration was considered inappropriately low given the degree of hypocalcemia.

Hematologic abnormalities included normocytic normochromic anemia (PCV, 30% [reference range, 37 to 55%]; RBC count, 3.79 X 10¹²/µl [reference range, 4.78 to 8.26 X 10¹²/µl]), thrombocytosis (platelet count, 1,229 X 10¹²/µl; reference range, 181 to 350 X 10¹²/µl), and a stress leukogram. Results of a trypsinogen-like immunoreactivity test were normal (52.1 µg/L; reference range, 5.0 to 35.0 µg/L). Fecal examination did not reveal any parasites or ova; results of a fecal Giardia antigen test were negative. Results of a urinalysis were normal, and the urine protein-to-creatinine ratio was 0.5.

Abdominal ultrasonography revealed copious peritoneal effusion and a mildly thickened small bowel wall. Evaluation of peritoneal fluid revealed a nucleated cell count of 132 cells/µl and total protein concentration of < 0.2 gm/dl, which was consistent with a pure transudate. Protein-losing enteropathy (PLE) was suspected on the basis of history, physical examination findings, and laboratory abnormalities. Although hepatic failure is a potential cause of hypoalbuminemia and hypocholesterolemia, hepatic failure was considered less likely because of the panhypoproteinemia, ultrasonographic findings, and clinical findings.

Initial treatment included administration of magnesium (total dose, 0.80 mEq/kg [0.36 mEq/lb] of body weight) in a balanced electrolyte solution administered at a maintenance fluid rate for 2 days. Sixteen hours after initiation of magnesium administration, serum magnesium concentration was 1.1 mg/dl, and 20 and 44 hours after initiation of treatment, serum magnesium concentration was within reference limits (1.7 mg/dl). Serum PTH concentration increased to 19.8 pmol/L after 44 hours of treatment, and serum ionized calcium concentration increased, although it was still slightly low (1.13 mmol/L). Serum 25OHD concentration remained low throughout this period (36 nmol/L).

On day 2, plasma (15 ml/kg [6.8 ml/lb]) was administered, and an exploratory laparotomy was performed. The liver and small intestine were biopsied. Histologic examination of the liver specimen revealed moderate hepatocellular atrophy suggestive of a vascular perfusion abnormality; however, arteriolar hyperplasia was not evident, and a shunting vessel was not seen grossly or ultrasonographically. Histologic exami-
nation of full-thickness intestinal biopsy specimens revealed mild to moderate lymphangiectasia in all segments of the small intestine and mild lymphocytic plasmacytic neutrophilic infiltrates in the duodenum and jejunum. A diagnosis of PLE secondary to inflammatory bowel disease and lymphangiectasia was made.

Treatment of the inflammatory bowel disease included administration of metronidazole (10 mg/kg [4.5 mg/lb], PO, q 12 h for 4 weeks) and l-glutamine (1 gm, PO, q 12 h for 8 weeks) and a change to a novel protein diet to determine whether the intestinal disease could be a consequence of severe food allergy. During a follow-up examination 5 months later, the dog was found to have gained 1 kg (2.2 lb) and was physically normal. Previous serum biochemical abnormalities had resolved (magnesium concentration, 1.9 mg/dl; ionized calcium concentration, 1.34 mmol/L; PTH concentration, 2.8 pmol/L; 25OHD concentration, 123 nmol/L).

Hypomagnesemia may be a result of renal loss, gastrointestinal tract loss, or decreased intake of magnesium or of alterations in the distribution of magnesium. Although renal tubular disorders, administration of diuretics or fluids, primary hyperparathyroidism, hyperthyroidism, pancreatitis, trauma, sepsis, hypothermia, and diabetic ketoacidosis have also been associated with hypomagnesemia, the dog described in the present report did not have any clinicopathologic evidence of these diseases. Changes in distribution of magnesium may develop after administration of glucose, insulin, or amino acids, with a resulting shift of magnesium into intracellular spaces. Citrate, such as is used in some blood products, may bind magnesium, decreasing its serum concentration. However, this dog did not receive any such products prior to detection of hypomagnesemia. Thus, in this dog, the hypomagnesemia most likely was a result of gastrointestinal tract loss of magnesium secondary to inflammatory bowel disease and lymphangiectasia.

The low serum PTH and vitamin D concentrations in this dog may also have contributed to the hypomagnesemia. Parathyroid hormone stimulates magnesium release from bone and resorption in the renal tubules, and both PTH and 1,25-dihydroxyvitamin D mediate intestinal absorption of magnesium. Development of hypomagnesemia is a complex process, because PTH and vitamin D concentrations affect magnesium concentration and vice versa.

Magnesium depletion in humans is associated with low serum PTH concentrations, and administration of magnesium can increase PTH concentration to normal. Anast et al., for instance, reported an 8-fold increase in serum PTH concentration 5 minutes after giving magnesium chloride (3 mg/kg, IV) to a woman with hypomagnesemia. Levi et al. obtained similar results in adult female dogs in which magnesium depletion had resulted in serum total magnesium concentrations < 1 mg/dl. In the dog described in the present report, the concurrent increases in serum magnesium, PTH, and calcium concentrations in response to magnesium supplementation, without any appreciable increase in 25OHD concentration, suggest that the dog had secondary hyperparathyroidism as a result of magnesium depletion.

In the parathyroid gland, low ionized calcium concentration activates the adenylate cyclase enzyme to produce the second messenger cyclic adenosine 3‘,5‘-monophosphate (cAMP). This stimulates secretion of PTH from granules stored in the parathyroid gland. Magnesium modulates adenylate cyclase activity at both active and inhibitory sites. At the active site, magnesium is complexed with ATP and acts as a substrate and catalyst for the adenylate cyclase enzyme. At the inhibitory site, magnesium and calcium compete for binding. A low magnesium concentration allows increased binding of calcium at the inhibitory site. This exacerbates the inhibitory effect of calcium on adenylate cyclase, leading to decreased cAMP generation and a blunted release of PTH.

A decreased response to PTH in bone and kidney has been demonstrated in hypomagnesemic humans. The decreased response to PTH at target tissues during magnesium deficiency is associated with a decrease in the activity of 2 second messenger systems. In magnesium-deficient humans and dogs, the adenylate cyclase system generates less cAMP. Magnesium depletion also decreases the activity of phosphoinositide-specific phospholipase C in human bone and kidney cell membranes. Blunted end-organ response to PTH was suspected in the dog described in the present report, because the serum ionized calcium concentration did not normalize despite high PTH concentration, although other factors such as hypovitaminosis D could have played a role in the persistence of mild ionized hypocalcemia.

Low serum ionized calcium concentration in patients with gastrointestinal tract disease can also result from decreased absorption of calcium as a result of binding by unabsorbed free fatty acids in the intestine and malabsorption of vitamin D. In this dog, the persistently low 25OHD concentration, perhaps secondary to fat malabsorption, may have contributed to the hypocalcemia; however, concentration of the most active form of vitamin D in intestinal absorption of calcium, 1,25-dihydroxyvitamin D, was not assayed. Interestingly, magnesium deficiency can cause a decrease in serum 1,25-dihydroxyvitamin D concentration by depressing PTH release and impairing renal vitamin D activation. In this dog, magnesium administration was associated with increased concentrations of PTH and calcium. Although crystalloids and plasma were also administered, these treatments would not be expected to increase PTH or calcium concentration; likewise, the citrate in plasma and crystalloid fluids may actually be expected to further lower magnesium and calcium concentrations. The improvement in PTH and calcium concentrations occurred following magnesium administration despite a persistently low 25OHD concentration. This suggests that low serum 25OHD concentration was not solely responsible for the development of hypocalcemia with hypomagnesemia in this patient. However, as was suggested in a previous description of hypomagnesemic and hypocalcemic dogs with PLE, hypovitaminosis D may contribute to hypocalcemia, as evidenced by persistence of mild hypocalcemia in this patient despite normaliza-
sclerosis. Assessment of magnesium concentration does not, however, add any new insights into the diagnosis and differential diagnosis of PLE. The authors have clearly delineated the clinical signs and underlying physiological mechanisms of PLE, and have provided a comprehensive review of the literature and clinical experience with this syndrome. They have also emphasized the importance of early recognition and appropriate intervention to prevent complications in animals with gastrointestinal disease. Magnesium concentration should be evaluated in these cases to enhance our ability to alleviate clinical signs and anticipate complications in animals with gastrointestinal tract disease. Magnesium concentration should be monitored in all dogs with gastrointestinal tract disease, especially those with PLE, anorexia, and weakness.

References