

Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire Terriers: five cases (1992–1998)

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Objective—To determine clinical and laboratory findings associated with protein-losing enteropathy, hypomagnesemia, and hypocalcemia in Yorkshire Terriers.

Design—Retrospective study.

Animals—5 purebred or crossbred Yorkshire Terriers with protein-losing enteropathy, hypomagnesemia, and hypocalcemia.

Procedure—Medical records were reviewed for dogs with protein-losing enteropathy, hypomagnesemia, and hypocalcemia.

Results—Of 8 dogs with these signs, 5 had Yorkshire Terrier breeding. Common findings were diarrhea, abdominal effusion, leukocytosis, neutrophilia, hypocalcemia (ionized calcium), hypomagnesemia, hypoproteinemia, hypoalbuminemia, hypocholesterolemia, and increased serum activity of aspartate aminotransferase.

Conclusions and Clinical Relevance—Yorkshire Terriers are at increased risk for development of protein-losing enteropathy with hypomagnesemia and decreased ionized calcium concentration. Hypomagnesemia and hypocalcemia may have a related pathogenesis involving intestinal loss, malabsorption, and abnormalities of vitamin D and parathyroid hormone metabolism. Serum electrolyte replacement may be required to avoid neurologic and metabolic problems. (*J Am Vet Med Assoc* 2000;217:703–706)

Decreased serum total calcium concentration is a common finding in dogs with **protein-losing enteropathy (PLE)** and is usually attributable to hypoalbuminemia and a decrease in the protein-bound, inactive fraction of serum calcium. Rarely, ionized calcium concentrations are decreased, indicating a decrease in the active fraction of serum calcium.¹ Gastrointestinal tract disease in humans² as well as dogs³ has been associated with hypomagnesemia. Hypomagnesemia and decreased ionized calcium concentration may be clinically important, resulting in a variety of neuromuscular, cardiac, and metabolic abnormalities. The purpose of the study reported here was to determine the clinical and laboratory findings in dogs with PLE, hypomagnesemia, and hypocalcemia.

Criteria for Selection of Cases

Medical records for dogs evaluated at the Veterinary Hospital of the University of Pennsylvania between 1992 and 1998 were reviewed to identify dogs

with a clinical diagnosis of PLE that were also hypocalcemic and hypomagnesemic. Hypocalcemia was determined on the basis of total calcium concentration corrected for serum albumin concentration or decreased ionized calcium concentration. Among these records, those of dogs with Yorkshire Terrier breeding were examined further.

Procedures

Data retrieved from medical records included history, signalment, physical examination findings, laboratory data, radiographic findings, results of hormone assays, histopathologic findings, and treatments.

Results

Of 69 dogs with a clinical diagnosis of PLE and a complete medical record, 10 were purebred Yorkshire Terriers, and 59 were crossbred or various other breeds. Four of 10 Yorkshire Terriers with PLE were hypocalcemic and hypomagnesemic. Four of 59 dogs of other breeds with PLE (including 1 Yorkshire Terrier cross) were hypocalcemic and hypomagnesemic. Serum ionized calcium concentrations were available for review in all 5 dogs with Yorkshire Terrier breeding.

The 5 dogs with Yorkshire Terrier breeding were referred to the veterinary teaching hospital to determine the cause of various complaints including vomiting and diarrhea, lethargy, dyspnea, and episodes described by the owners as twitching or seizures. Ages ranged from 5 to 8 years, and body weight of the dogs ranged from 3.0 to 5.4 kg (6.6 to 11.9 lb). Three dogs were castrated males, 1 was a spayed female, and 1 was a sexually intact female.

Owners reported that 4 of the 5 dogs had diarrhea, 3 had twitching episodes, and 2 had dyspnea. Duration of illness ranged from 3 days to 2 months. Two dogs had been treated with antimicrobials and corticosteroids before referral, with no improvement reported by the owners; the other 3 dogs had not received any treatment.

Physical examination revealed respiratory tract abnormalities in 3 of the 5 dogs: 3 dogs were tachypneic, 2 appeared to be in respiratory distress, and 1 had dull lung sounds in the ventral lung fields. Three dogs had a distended abdomen or a palpable fluid wave detected by use of abdominal palpation. Two dogs had tacky mucous membranes, 1 had pale mucous membranes, and 1 was tachycardic. Body condition scoring was performed for all dogs (scale, 1 to 5 [1 = cachectic, 5 = obese]); a score of 3 was assigned to 4 dogs, and a score of 2 was assigned to 1 dog. All other results of physical examination were within reference limits.

Complete blood cell count, serum biochemistry

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analysis, and urinalysis were performed on all dogs. All dogs had leukocytosis; the leukogram was characterized by mature neutrophilia in 4 dogs (range, 20,000 to 28,000 cells/ μ l; reference range, 3,600 to 12,500 cells/ μ l) and neutrophilia with a left shift in 1 dog (14,000 cells/ μ l; 170 band neutrophils/ μ l). One dog had lymphopenia (300 cells/ μ l; reference range, 1,000 to 4,800 cells/ μ l). Serum biochemical analyses revealed the following abnormalities in all 5 dogs: hypocalcemia (range, 2.7 to 4.2 mg/dl; reference range, 9.7 to 12.2 mg/dl), hypoproteinemia (range, 1.9 to 2.8 g/dl; reference range, 4.8 to 6.6 g/dl), hypoalbuminemia (range, 1.0 to 1.2 g/dl; reference range, 2.3 to 3.9 g/dl), hypoglobulinemia (range, 0.8 to 2.0 g/dl; reference range, 2.5 to 4.3 g/dl), hypocholesterolemia (range, < 45 to 83 mg/dl; reference range, 126 to 359 mg/dl), and increased activity of serum **aspartate aminotransferase** (AST; range, 71 to 159 U/L; reference range, 1 to 37 U/L). Three dogs had increased activity of serum **alanine aminotransferase** (ALT; range, 69 to 187 U/L; reference range, 3 to 50 U/L), and 1 had the following abnormalities: hypoglycemia, hyponatremia, hypokalemia, hyperchloremia, and increased activity of serum **γ -glutamyl transferase** (GGT). Results of urinalyses were unremarkable in all 5 dogs. Ionized calcium concentration was low (range, 0.50 to 0.76 mmol/L; reference range, 1.13 to 1.33 mmol/L), as was total serum magnesium concentration (range 0.5 to 1.0 mEq/L; reference range, 1.7 to 2.5 mEq/L).

Coagulation screens were performed on 4 of the 5 dogs. Prothrombin and partial thromboplastin times were within reference ranges for all dogs. Results of venous blood gas measurements were unremarkable except in 1 dog that had metabolic acidosis (pH 7.286; bicarbonate concentration, 18.5 mmol/L; base deficit, 8.1). Pulse oximetry was performed in 4 dogs; results were within reference range in 2 dogs (oxygen saturation, 94 and 96%) and were abnormal in 2 dogs (85 and 80%). The 2 dogs with abnormal pulse oximetry values also had arterial blood gas analyses that revealed hypoxemia (PaO₂, 50 and 62 mm Hg) and hypocapnia (PaCO₂, 25.5 and 26.6 mm Hg).

Thoracic radiographs were obtained for 3 of the 5 dogs. Two dogs had pleural effusion, and 1 of these dogs had evidence of a focal alveolar pattern in the right cranial lung lobe. One dog had a diffuse interstitial pattern. Thoracocentesis was performed on 2 of the dogs; fluid and cytologic analysis determined the fluid to be a pure transudate in both dogs. All dogs had abdominal ultrasonography performed, and all had anechoic abdominal effusion. Three dogs had evidence of thickened mucosa in the small intestine.

For definitive diagnosis of the underlying cause of the PLE, intestinal biopsy specimens were evaluated histologically for 4 dogs (the owner of 1 dog refused permission for biopsy). Full-thickness biopsy specimens were obtained via laparotomy from 2 dogs, whereas endoscopy was used to obtain biopsy specimens for 2 dogs. In both dogs that underwent laparotomy, the small intestinal walls appeared thickened, and gross dilatation of the lacteals was seen in 1 dog. One dog that underwent endoscopy had hyperemic and edematous gastric and duodenal mucosa, whereas

the other dog had irregular white nodules compatible with dilated lacteals in the mucosa of the duodenum. Lymphocytic-plasmacytic enteritis was detected in all 4 dogs, and 3 dogs also had lymphangiectasia. The dog in which lymphangiectasia was not diagnosed underwent endoscopy.

Parathyroid hormone (PTH) concentration was evaluated in 3 of the 5 dogs and was increased, compared with the reference range (range, 35.6 to 41 pmol/L; reference range, 2 to 13 pmol/L). Vitamin D₃ concentrations were also determined in 2 dogs and were decreased, compared with the reference range (3 and 60 nmol/L; reference range, 82 to 285 nmol/L).

Treatment of these dogs while in the hospital consisted of administration of isotonic crystalloid fluids^a (2.0 to 4.0 ml/kg [0.9 to 1.8 ml/lb] of body weight/h, IV) for correction and maintenance of hydration and administration of synthetic colloid^b (1.0 ml/kg/h [0.5 ml/lb/h], IV) or fresh frozen plasma (10 ml/kg [4.5 ml/lb], IV, q 12 h) or both, to increase oncotic pressure. All dogs also received constant rate infusions of magnesium sulfate (1.0 mEq/kg/d [0.5 mEq/lb/d], IV) and calcium gluconate solution (10 mg/kg/h, IV) until correction of the electrolyte abnormalities was achieved. All dogs were treated with novel diets that were either low-fat^c or hypoallergenic.^d For the 4 dogs that underwent biopsy, immunosuppressive drugs were administered to treat the underlying gastrointestinal tract disease after the biopsy reports were received; the remaining dog was given an immunosuppressive drug, although biopsy was not performed. Four of the dogs were initially treated with prednisone (0.9 to 1.7 mg/kg [0.4 to 0.8 mg/lb] of body weight, PO, q 12 h), and 1 of these dogs was later treated with azathioprine (2.2 mg/kg [1.0 mg/lb], PO, q 48 h) in addition to prednisone. The remaining dog was administered cyclosporine (10 mg/kg, PO, q 24 h) instead of prednisone. Response to treatment was variable; 3 dogs had long-term survival (range, 12 to 38 months after initial diagnosis). One dog died within 1 month of diagnosis because of lack of clinical response and suspected pulmonary thromboembolism. The other dog was euthanized 8 months after diagnosis because of inadequate response to treatment and recurrent episodes of suspected pulmonary thromboembolism.

Comparison of the group of 4 purebred Yorkshire Terriers to the rest of the hospital population revealed an odds ratio of 10.1 (95% confidence interval (CI), 5.2 to 18.8) for development of PLE in Yorkshire Terriers. In addition, compared with dogs of other breeds with PLE, Yorkshire Terriers with PLE were 9.2 times more likely to develop hypomagnesemia and hypocalcemia (95% CI, 1.8 to 46.4).

Discussion

Diagnosis of PLE can be made by identification of characteristic clinicopathologic changes and elimination of liver disease and protein-losing nephropathy as potential causes of hypoalbuminemia. The dogs described in the study reported here had clinical signs and serum biochemical abnormalities consistent with PLE. Other than decreased serum cholesterol and albu-

min concentration, which are commonly observed in dogs with PLE, and transient hypoglycemia in 1 dog, abnormalities of other indicators of liver function (BUN, total bilirubin concentration, and coagulation tests) were not observed. In addition, none of these dogs had evidence of pathologic proteinuria that would be expected with protein-losing nephropathy. Finally, a potential underlying cause of PLE was identified in 4 of 5 dogs via examination of gastrointestinal tract biopsy specimens; lymphocytic-plasmacytic enteritis was evident in all 4 dogs, and lymphangiectasia was evident in 3 of 4 dogs. Although useful in the diagnosis of protein-losing enteropathy, fecal α_1 protease inhibitor concentrations were not determined in these dogs.

Similar clinical findings in dogs of breeds other than Yorkshire Terriers have been detected by the authors including 1 each of Maltese, Samoyed, and mixed-breed dogs. Comparison of the group of 4 pure-bred Yorkshire Terriers to the rest of the hospital population revealed an odds ratio of 10.1 for development of PLE in Yorkshire Terriers, and compared with dogs of other breeds with PLE, Yorkshire Terriers with PLE were 9.2 times more likely to develop hypomagnesemia and hypocalcemia. Predilection to lymphangiectasia in Yorkshire Terriers has been suggested,¹ and hypomagnesemia associated with lymphangiectasia has been reported in humans.² To the authors' knowledge, however, concurrent hypomagnesemia and hypocalcemia associated with gastrointestinal tract disease have not been reported in dogs. Cause of these electrolyte abnormalities in Yorkshire Terriers with PLE is unknown. It is possible that the nature or severity of the gastrointestinal tract disease observed in this breed, genetic predilection, common environmental factors, or breed-related peculiarities of calcium and magnesium metabolism may play a role.

Hypomagnesemia may be attributable to increased urinary or gastrointestinal tract losses, decreased intake of magnesium, or alterations in distribution of magnesium.⁴ Serum magnesium concentrations are lower in dogs with gastrointestinal tract disease, compared with dogs that have other types of critical illness.³ Such gastrointestinal tract losses develop as a result of chronic diarrhea and malabsorptive syndromes.

Dogs with chronic diarrhea or vomiting may develop hypomagnesemia attributable to the loss of gastrointestinal tract fluids that typically contain high concentrations of magnesium.⁵ Further losses of magnesium may develop with increased gastrointestinal tract permeability, which may be observed with PLE. Although its effects on calcium absorption are more substantial, vitamin D affects magnesium absorption from the gastrointestinal tract; therefore, decreased vitamin D may cause decreased magnesium absorption.⁶ Malabsorptive syndromes characterized by steatorrhea are most highly associated with hypomagnesemia in humans.⁷ Although the malabsorptive disorder in the Yorkshire Terriers of the study reported here was not fully characterized with tests for fat malabsorption, pulmonary hydrogen gas excretion, or serum cobalamin and folate concentrations, prospective gathering of such information may be helpful.

Other causes of magnesium loss include renal tubular disorders, diuresis, primary hyperparathyroidism, hyperthyroidism, and diabetic ketoacidosis.⁸ None of the dogs in our study had historical or clinicopathologic evidence of these diseases. Changes in distribution of magnesium may develop after administration of glucose, insulin, or amino acids, which causes a shift to intracellular spaces. Similar to the effect on calcium, large doses of citrate (eg, massive blood transfusion or cardiopulmonary bypass) bind magnesium, decreasing its serum concentration. Although hypomagnesemia worsened in 1 of the dogs described in our study after receiving plasma, hypomagnesemia was detected prior to administration of blood products in all dogs. Trauma, sepsis, and hypothermia are also associated with hypomagnesemia, likely because of catecholamine stimulation of lipolysis and intracellular chelation of magnesium by free fatty acids. Similarly, acute pancreatitis may result in magnesium sequestration in areas of fat necrosis where insoluble salts of magnesium are formed.⁹ Although 1 dog had microscopic lesions that suggested chronic pancreatitis, none of the dogs had historical or physical examination findings compatible with pancreatitis.

The most commonly recognized manifestations of hypomagnesemia include clinical signs attributable to neuromuscular and cardiovascular abnormalities and metabolic derangements. Neuromuscular manifestations of hypomagnesemia in humans include weakness, tremor, hyperreflexia, and tetany.¹⁰ Three of 5 dogs in the study reported here had clinical signs of tremor that may have been related to hypomagnesemia or hypocalcemia. Cardiovascular signs in humans include electrocardiographic changes, arrhythmias, vasoconstriction, and possibly hypercoagulability.¹¹ There was a high clinical suspicion for pulmonary thromboembolism in 2 of 5 dogs in the study reported here. Although pulmonary thromboembolism may have been attributable to a hypercoagulable state induced by loss of antithrombin III concurrent with albumin loss, or in 1 dog, administration of corticosteroids, magnesium depletion may have had an additional role in the pathogenesis of this complication. Metabolic abnormalities associated with hypomagnesemia include refractory hypokalemia and hypocalcemia.¹²

Clinically unimportant hypocalcemia may be detected in dogs with diseases of the small intestine associated with panhypoproteinemia and is likely attributable to decrease in the protein-bound or inactive fraction of serum calcium.¹ However, the dogs in the study reported here had low total serum calcium concentration despite correction for hypoalbuminemia. In addition, the dogs had moderately to severely decreased serum concentrations of ionized calcium, indicating that the active fraction of serum calcium was decreased. Calcium malabsorption may develop alone or in addition to vitamin D deficiency attributable to fat-soluble vitamin malabsorption. Hypomagnesemia may also contribute to hypocalcemia via several mechanisms. Magnesium deficiency may impair function of the parathyroid glands by causing abnormal synthesis or release of PTH.¹³ Evidence also exists for reduced

responsiveness to PTH by skeletal and renal tissues.^{14,15} Active vitamin D may also be decreased because of the requirement for magnesium for hydroxylation of vitamin D in the kidneys.^{16,17}

Serum PTH concentration was increased in all 3 dogs that were tested. Increased PTH concentration would appear to be an appropriate response to hypocalcemia; however, it is possible that the magnitude of PTH response to hypocalcemia was less than would be expected in a normomagnesemic animal. Therefore, an increased PTH concentration cannot necessarily be interpreted to reflect normal parathyroid gland function. Vitamin D₃ concentrations were low in both dogs that were tested. If fat-soluble vitamin malabsorption was the sole cause of hypocalcemia in these dogs, vitamin K deficiency, with resulting prolongation in prothrombin time, would likely have developed prior to or concurrent with clinical signs of vitamin D deficiency. In addition, despite the role of magnesium in the generation of active vitamin D, a study of hypomagnesemia associated with gastrointestinal tract disease in humans found that plasma vitamin D concentrations remained low after correction of hypomagnesemia, suggesting an alternate cause for decreased vitamin D concentration.¹⁸ It is possible that both mechanisms are involved in the pathogenesis of decreased vitamin D in Yorkshire Terriers with PLE.

^aNormosol-R, Abbott Laboratories, North Chicago, Ill.

^bHetastarch, Abbott Laboratories, North Chicago, Ill.

^cWaltham canine low fat canned diet, Pedigree Petfoods, Melton, England.

^dPurina CNM-HA dry diet, Ralston Purina Co, St Louis, Mo.

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