Suspected primary hypoparathyroidism in a domestic ferret (Mustela putorius furo)

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Case Description—A 4-year-old castrated male domestic ferret (Mustela putorius furo) was referred to the Exotic Pet Service at Cornell University Hospital for Animals because of intermittent seizures. The ferret had been examined by the referring veterinarian 3 weeks prior to referral because of seizures that occurred every 2 or 3 days. Main findings of a routine CBC and plasma biochemical analysis performed by the referring veterinarian included hypocalemia (4.7 mg/dL; reference interval, 1 8.1 to 9.5 mg/dL) and hyperphosphatemia (13.4 mg/dL; reference interval, 5.6 to 8.7 mg/dL). The blood glucose concentration (105 mg/dL) was within the reference interval. The ferret was treated by administration of calcium carbonate (53 mg/kg [24.1 mg/lb], PO, q 12 h) and dihydrotachysterol (0.02 mg/kg/d [0.009 mg/lb/d], PO). Attitude of the ferret improved and seizures ceased as blood calcium concentrations increased. The ferret was reexamined because of seizures approximately 1 year after oral maintenance administration of dihydrotachysterol and calcium was initiated. The ferret responded well to emergency and long-term treatment but then was lost to follow-up monitoring. The ferret died approximately 2 years after the initial evaluation and treatment. Hypertrophic cardiomyopathy was diagnosed during necropsy, but the parathyroid glands could not be identified.

Clinical Relevance—To the authors’ knowledge, primary hypoparathyroidism has not previously been reported in a ferret. The condition should be considered for ferrets with hypocalcemia and hyperphosphatemia without azotemia. Treatment with dihydrotachysterol and oral supplementation of calcium appeared to be a viable option for long-term management.

A 4-year-old 1.17-kg (2.6-lb) castrated male domestic ferret (Mustela putorius furo) was referred to the Exotic Pet Service at Cornell University Hospital for Animals because of intermittent seizures. The ferret had been examined by the referring veterinarian 3 weeks prior to referral because of seizures that occurred every 2 or 3 days. Main findings of a routine CBC and plasma biochemical analysis performed by the referring veterinarian included hypocalemia (4.7 mg/dL; reference interval, 1 8.6 to 10.5 mg/dL) and hyperphosphatemia (13.4 mg/dL; reference interval, 5.6 to 8.7 mg/dL). The blood glucose concentration (105 mg/dL) was within the reference interval. The ferret was treated by administration of calcium carbonate (53 mg/kg [24.1 mg/lb], PO, q 12 h). No further seizure activity was detected until 48 hours prior to referral, when seizure activity was again evident. Lethargy, progression of seizure activity, and abnormal behavior (biting, aggression, and fear behavior) were also observed at that time. The ferret had not been vaccinated against rabies virus or canine distemper virus. The ferret was fed a commercially available balanced chow, and toxin exposure was not suspected.

Initial evaluation at our veterinary teaching hospital (day 1) revealed that the ferret’s mentation varied from periods of activity to periods of lethargy with minimal response to stimuli. No other remarkable abnormalities were detected during physical examination. Plasma biochemical analysis revealed that the PCV and total solids, blood glucose, and BUN concentrations were within reference intervals. The plasma total calcium concentration was low (4.3 mg/dL; reference interval, 1 1.18 to 2.37 mg/dL; reference interval for cats, 1.07 to 1.47 mg/dL). On the basis of the reference intervals for dogs and cats and an ionized calcium concentration of 1.17 mmol/L previously reported for a healthy ferret, the ionized calcium concentration in the ferret described here was considered to be low. Findings on ECG were within anticipated limits, except for a few brief periods of bradycardia (heart rate range, 120 to 200 beats/min; reference interval, 1 200 to 400 beats/min).

Calcium gluconate (2 mg/kg [0.9 mg/lb]) diluted in 20 mL of saline (0.9% NaCl) solution was administered IV over a period of 20 minutes, with continuous ECG monitoring. The ionized calcium concentration was assessed 4 hours after the calcium gluconate infusion and was essentially unchanged (0.48 mmol/L). Therefore, calcium gluconate diluted in saline solution was administered as a constant rate infusion at a...
rate of 2 mg/kg/h (0.9 mg/lb/h), with continuous ECG monitoring. A single dose of sucralfate\textsuperscript{e} (22 mg/kg [10 mg/lb], PO) was administered because of the risk for abdominal discomfort and gastric ulcers following calcium administration.

On the morning of day 2 (approx 9 hours after the initial evaluation), the ionized calcium concentration had increased to 0.87 mmol/L. The ferret remained lethargic but was increasingly responsive to stimuli. Oral administration of calcium carbonate was resumed at the previously recommended dose (33 mg/kg, PO, q 12 h). The constant rate infusion of calcium gluconate was continued, and a single dose of vitamin D\textsuperscript{\textregistered} was administered (300 U/kg [136.4 U/lb], IM).

Attitude and appetite of the ferret continued to improve during the subsequent 5 days. On day 3, the total calcium concentration was 7.8 mg/dL, ionized calcium concentration was 1.1 mmol/L, and phosphorus concentration was 10.9 mg/dL. On day 4, IV administration of calcium gluconate was discontinued, and SC administration of calcium carbonate was initiated (25.6 mg/kg [11.6 mg/lb], q 12 h). On day 5, total and ionized calcium concentrations decreased to 5.6 mg/dL and 0.69 mmol/L, respectively, and the phosphorus concentration increased to 11.9 mg/dL. Results of a CBC and urinalysis performed on day 5 were within reference limits, and abdominal ultrasonography findings were unremarkable, except for 2 small cortical cysts in the left kidney. The PCV decreased considerably from 42% on day 4 to 30% on day 5 (reference interval\textsuperscript{1}, 36% to 48%), and melena was observed on day 6. Bismuth subsalicylate\textsuperscript{f} (9.1 mg/kg [4.1 mg/lb], PO, q 8 h), metronidazole\textsuperscript{f} (19.7 mg/kg [9.0 mg/lb], PO, q 12 h), and amoxicillin\textsuperscript{f} (10.3 mg/kg [4.7 mg/lb], PO, q 12 h) were added to the treatment regimen at that time because of concerns about gastric ulcers secondary to clinical gastroenteritis attributable to \textit{Helicobacter} spp infection or calcium administration.

Serum obtained during the initial examination on day 1 was submitted to another laboratory\textsuperscript{1} for determination of ionized calcium and PTH concentrations. The ionized calcium concentration was 0.47 mmol/L (reference interval for dogs, 1.25 to 1.43 mmol/L; reference interval for cats, 1.0 to 1.44 mmol/L), and the PTH concentration was 2.30 pmol/L (reference interval for dogs, 0.3 to 5.8 pmol/L; reference interval for cats, 0.4 to 2.5 pmol/L). Although the reference interval for PTH concentrations in ferrets has not been established, a serum PTH concentration of 13 pmol/L was previously reported\textsuperscript{2} in a healthy ferret. Thus, the PTH concentration in the ferret described here was interpreted as low or in the low part of the reference interval.

On day 8, the ionized calcium (1.21 mmol/L) and total calcium (9.4 mg/dL) concentrations had returned within the reference interval, and the phosphorus concentration had decreased to 10.2 mg/dL. The PCV (24%) also had continued to decrease. Treatment with famotidine\textsuperscript{g} (1 mg/kg [0.45 mg/lb], SC, q 24 h) and dihydrotachysterol\textsuperscript{f} (0.02 mg/kg [0.009 mg/lb], PO, q 48 h) was initiated.

On day 11, the total calcium concentration was 7 mg/dL and the phosphorus concentration was 11 mg/dL. Subcutaneous administration of calcium gluconate was discontinued, and the ferret was discharged to the owner with instructions to continue administration of metronidazole, amoxicillin, and bismuth subsalicylate for an additional 7 days. Administration of dihydrotachysterol and calcium carbonate were to be continued at the same dose and frequency of administration until further notice.

On day 16, the ferret’s total calcium concentration was 7.7 mg/dL and the phosphorus concentration was 13.7 mg/dL. Treatment with aluminum hydroxide\textsuperscript{f} (34 mg/kg, [15.5 mg/lb], PO, q 12 h) was initiated because of the persistent hyperphosphatemia. On day 34, the total calcium concentration was 10.1 mg/dL and the ionized calcium concentration was 1.05 mmol/L; the phosphorus concentration remained high at 10.8 mg/dL. The aluminum hydroxide dosage was increased (51.3 mg/kg [23.3 mg/lb], PO, q 12 h), and the frequency of dihydrotachysterol administration was decreased to every 7 days.

The ferret was examined approximately 9 weeks later (day 104) by the referring veterinarian. The calcium concentration was low (6.3 mg/dL), and the phosphorus concentration was high (13.8 mg/dL). The frequency of dihydrotachysterol administration was changed to every 5 days, but oral administration of calcium carbonate and aluminum hydroxide were not altered.

During the next year, the owner did not detect any seizure episodes. Muscle tremors were evident in the ferret when the frequency of dihydrotachysterol administration was changed from every 5 days to every 7 days; however, these resolved when administration reverted to every 5 days.

On day 368, the ferret was evaluated by the referring veterinarian because of vomiting, inappetence, melena, decreased activity, and a seizure episode. The client reported no changes in the treatment regimen, husbandry, or diet before the seizure episode. Results of a CBC and biochemical analysis revealed leukocytosis (24 X 10\textsuperscript{3} leukocytes/µL; reference interval\textsuperscript{1}, 5.6 X 10\textsuperscript{3} leukocytes/µL to 10.8 X 10\textsuperscript{3} leukocytes/µL) with neutrophilia (17.040 X 10\textsuperscript{3} neutrophils/µL; reference interval\textsuperscript{1}, 616 X 10\textsuperscript{3} neutrophils/µL to 7,020 X 10\textsuperscript{3} neutrophils/µL) and lymphocytosis (6,960 X 10\textsuperscript{3} lymphocytes/µL; reference interval\textsuperscript{1}, 1,728 X 10\textsuperscript{3} lymphocytes/µL to 4,704 X 10\textsuperscript{3} lymphocytes/µL), high activities of alanine aminotransferase (311 U/L; reference interval, 65 to 128 U/L) and aspartate aminotransferase (793 U/L; reference interval\textsuperscript{1}, 70 to 100 U/L), hypokalemia (6.2 mg/dL), and hyperphosphatemia (18.0 mg/dL). Radiography revealed increased pulmonary opacity but no other abnormalities.

On day 369, the ferret had no improvement and was brought to the emergency service of our veterinary teaching hospital. Physical examination revealed that the ferret was lethargic but responsive to stimuli. Bruxism, melena, bradycardia (120 beats/min), tachypnea (80 breaths/min), and dyspnea were detected. A few muscle tremors and seizure activity were also observed. Results of cardiac auscultation were unremarkable. Auscultation of the lungs revealed an increase in respiratory rate and wheezes. The ionized calcium concentration was 0.63 mmol/L. Treatment included IV ad-
Discussion

Primary hypoparathyroidism is defined by a relative or absolute deficiency of PTH, which leads to a decrease in serum calcium concentration and an increase in serum phosphorus concentration. Naturally occurring hypoparathyroidism is rare in dogs and cats, with most cases classified as idiopathic. To the authors’ knowledge, primary hypoparathyroidism has not been previously reported in a ferret.

Differential diagnoses for hypocalcemia include hypoparathyroidism, hypomagnesemia, pseudohypoparathyroidism, hypoalbuminemia, renal disease, nutritional secondary hyperparathyroidism, and tumor lysis syndrome. Only hypoparathyroidism results in a combination of low serum calcium concentration, high serum phosphorus concentration, and appropriate renal function in the face of low PTH concentrations, as was seen in the ferret of the present report.

Magnesium deficiency can inhibit the release and action of PTH, which results in hypocalcemia. Although the magnesium concentration was not determined during the initial referral hospitalization, magnesium concentration during the second referral hospitalization appeared to be within or slightly higher than the reference interval for dogs (1.6 to 2.3 mg/dL) and European polecats (1.36 to 2.82 mEq/L). To our knowledge, reference intervals for blood magnesium concentrations in domestic ferrets have not been determined.

Pseudohypoparathyroidism can resemble hypoparathyroidism and has been reported in a ferret. However, pseudohypoparathyroidism is characterized by a lack of response to high PTH concentrations rather than a deficiency of PTH. In the ferret of the present report, PTH concentrations were decreased rather than increased in the face of severe hypocalcemia. Although reference intervals for PTH concentration have not been established in ferrets, the ferret of the present report had concentrations within the reference intervals for dogs and cats and lower than those reported in a healthy ferret.

Chronic renal disease was considered as a possible cause of hypocalcemia in the ferret of the present report. Serum phosphorus concentrations typically parallel...
SUN concentrations in dogs and cats with chronic renal failure. Thus, hyperphosphatemia is common in azotemic patients but unexpected in patients with nonazotemic renal disease. Azotemia was not detected in the ferret during initial hospitalization, despite a severely high phosphorus concentration. In addition, urinalysis results were within anticipated limits, which indicated appropriate renal function. Ultrasonography of the kidneys during the initial referral hospitalization did not reveal abnormalities, except for 2 small cysts in the left kidney, which are common and clinically unimportant in domestic ferrets. During the second referral hospitalization, plasma biochemical analysis results revealed an increase in the BUN concentration with a creatinine concentration within the reference interval, which is inconsistent with hyperphosphatemia attributable to renal disease. The increase in BUN concentration was thought to be prerenal and secondary to dehydration caused by vomiting and diarrhea along with increased synthesis as a result of extra protein intake attributable to hemorrhage into the gastrointestinal tract. Anemia developed during the initial referral hospitalization and was attributed to gastrointestinal blood loss rather than renal disease, given that it improved once melena resolved. Subclinical infection with Helicobacter mustelae was suspected as the cause of melena, whereas stress caused by concurrent disease can lead to exacerbation of gastritis and ulcers in domestic ferrets. The recommended treatment for gastroenteritis attributable to Helicobacter infection in ferrets is a combination of amoxicillin, metronidazole, and bismuth subsalicylate; treatment with famotidine or sucralfate is recommended for ferrets with a decreased appetite and melena.

Although renal disease was not evident prior to death, postmortem examination revealed bilateral moderate interstitial nephritis with proteinosis and a unilateral chronic infarct on the left kidney. The necropsy was performed 1 year after the final CBC and plasma biochemical analysis. During that time period, renal disease could have developed as a primary disease process or secondary to the cardiac abnormalities.

The most common clinical signs in dogs with hypoparathyroidism are seizures, muscle fasciculations, facial rubbing, an ataxic and stiff gait, and behavioral changes (including aggression associated with pain). Except for facial rubbing, the clinical signs during the initial evaluation of the ferret of the present report were similar to those in dogs.

Treatment of primary hypoparathyroidism consists of emergency treatment for seizures, short-term maintenance therapy after tetany, and long-term maintenance therapy. The first phase involves treatment of hypocalcemic tetany with calcium gluconate administered slowly over a period of 10 to 30 minutes, with continuous ECG monitoring. Response to treatment is usually noticed within minutes after initiating the infusion. A conservative dose of 2 mg/kg was chosen for the initial bolus during the first referral hospitalization because of the lack of published guidelines for management of hypocalcemia in ferrets and the severe hyperphosphatemia. Intravenous administration of a higher dose of calcium after initial evaluation would likely have resulted in a more rapid increase in the blood calcium concentration. Because the ionized calcium concentration and clinical condition were essentially unchanged after the initial bolus during the first referral hospitalization, calcium gluconate was administered as a constant rate infusion at a rate of 2 mg/kg/h (ie, 48 mg/kg/d). This dosage is closer to the recommended constant rate infusion dosage of 60 to 90 mg/kg/d (27.3 to 40.9 mg/lb/d), which may explain the improvement in clinical condition and blood concentrations of total and ionized calcium on days 2 and 3. During the second referral hospitalization, administration of the initial calcium gluconate bolus resulted in substantial improvement in clinical condition and resolution of clinical signs. For this reason, constant rate infusion of calcium gluconate was not used.

Once the clinical signs of hypocalcemia are controlled, short-term maintenance therapy should be initiated, with calcium gluconate administered SC every 6 to 8 hours at the dose required for IV administration to control seizures. Frequency of administration of calcium gluconate should be reduced to every 12 hours once calcium concentrations have been regulated for 2 to 3 days. In the ferret of the present report, calcium gluconate was administered SC at a dosage of 45 to 50 mg/kg/d (20.5 to 22.7 mg/lb/d) once improvement in clinical condition or an increase in blood calcium concentrations was detected. When long-term maintenance therapy is initiated via oral administration of vitamin D and calcium during posttetany treatment, the dosage of parenterally administered calcium can be tapered and eventually discontinued. Calcium concentrations should be assessed frequently during the transition period because response to oral administration of vitamin D is variable. Calcium concentrations should be maintained between 8 and 9 mg/dL. If the calcium concentration is < 8 mg/mL, the dose of parenterally administered calcium or vitamin D should be increased. If the calcium concentration is > 9 mg/mL, the dose of parenterally administered calcium should be reduced. Although calcitriol is the vitamin D product of choice for treatment of hypocalcemia, dihydrotachysterol was selected for the ferret of the present report because it was available as a solution, which allowed for more accurate dosing of this small patient. Calcium carbonate was initially selected as the calcium product to be used for oral administration because of the availability and ease of administration as well as the high percentage of elemental calcium in the preparation. In addition, calcium carbonate binds phosphorus in the gastrointestinal tract. Aluminum hydroxide was used as an additional phosphorus binder to reduce persistently high blood phosphorus concentrations.

During and after the second referral hospitalization, oral administration of calcium gluconate solution was temporarily used in an attempt to more accurately and easily provide calcium supplementation. Because calcium gluconate contains only 10% elemental calcium, the solution was used for a short period. Weekly monitoring of calcium concentrations allows for adjustment of the vitamin D dose to prevent hypocalcemia or hypercalcemia. Once the calcium concentration is stable and a maintenance therapy regimen that is compatible with the ferret's clinical condition is established, the solution can be discontinued if treatment for vitamin D deficiency is no longer needed.
has been established, the calcium concentration should be reassessed every 3 to 4 months. In dogs and cats with hypoparathyroidism, supplementation of vitamin D usually must be provided for the remainder of an animal's life, whereas supplementation of calcium can eventually be discontinued, given that calcium content of commercial diets is usually adequate for maintaining blood calcium concentrations. Long-term monitoring of calcium concentrations, together with appropriate treatment, can lead to a normal life expectancy.

Given that dosages of medications used for long-term management in the ferret of the present report were extrapolated from those used in dogs and cats, frequent monitoring of blood calcium concentration was important. Failure to closely monitor calcium concentrations appears to have resulted in hypocalcemia, considering that the ferret had episodes of muscle tremors during the interval between referral hospitalizations and developed tetany before the second referral hospitalization. Severe hypercalcemia was not detected during treatment, and there was no evidence of calcification of the soft tissues during necropsy.

In humans, hypoparathyroidism rarely is associated with reversible congestive heart failure or dilated cardiomyopathy. The lack of hypocalcemic cardiomyopathy reports in the veterinary literature may be attributable to early detection and treatment of hypocalcemia, given that prolonged hypocalcemia appears to be required to induce myocardial decompensation. Because of the central role of calcium in myocardial contractile function, clinical and cardiac hemodynamic improvement can only be achieved by correction of serum calcium deficiency. The ferret in the present report did not have ECG changes routinely associated with hypocalcemia. However, the increased pulmonary opacity on thoracic radiographs obtained by the referring veterinarian as well as the increase in respiratory effort and respiratory wheezes detected at the time of the second referral hospitalization could have been consistent with pulmonary edema secondary to congestive heart failure associated with prolonged hypocalcemia. Resolution of these signs once the blood calcium concentration increased and without treatment specific for cardiac disease could suggest reversible hypocalcemic cardiomyopathy, as has been described in humans. Thoracic radiography and echocardiography were not performed during either hospitalization period to further investigate cardiac function. Hypertrophic cardiomyopathy was detected during necropsy approximately 2 years after hypoparathyroidism was first diagnosed in the ferret, and congestive heart failure was suspected to be the primary cause of death. Hypertrophic cardiomyopathy is not uncommon in ferrets, but the condition in ferrets remains poorly described. Hyperparathyroidism has been recognized as a cause of hypertrophic cardiomyopathy in humans. The relationship between hypoparathyroidism and hypertrophic cardiomyopathy in the ferret of the present report remains unknown.

Hypercalcemia, nephrocalcinosis, urolithiasis, and reduced renal function have been reported in humans treated for chronic hypoparathyroidism, with decreased creatinine clearance evident in 80% of humans treated for ≥ 2 years. Calciuria was not evaluated in the ferret of the present report, but nephrocalcinosis or urolithiasis was not detected during necropsy, despite persistent hyperphosphatemia. The BUN concentration increased in the ferret following repeated treatment with dihydrotachysterol and calcium; however, this was attributed to vomiting, dehydration, and clinical gastritis or gastrointestinal caused by Helicobacter infection.

The parathyroid glands were not detected during postmortem evaluation. In a review of 28 dogs with hypoparathyroidism, the parathyroid glands were difficult or impossible to locate during gross postmortem examination. When the parathyroid glands were detected, the most common histologic finding was lymphocytic parathyroiditis.

Primary hypoparathyroidism should be considered in animals with hypocalcemia and hyperphosphatemia without azotemia. Treatment with dihydrotachysterol and oral administration of calcium appeared to be a viable option to normalize calcium concentrations but failed to normalize phosphorus concentrations in the ferret of the present report. The long-term prognosis is dependent on adequate monitoring of blood calcium concentrations and client compliance with treatment.

References


Concentrations of stromal cell-derived factor-1 in serum, plasma, and synovial fluid of horses with osteochondral injury

David C. Dymock et al

Objective—To determine whether stromal cell-derived factor-1 (SDF-1) concentrations in serum, plasma, and synovial fluid differed among untrained, race-trained, and osteochondral-injured Thoroughbred racehorses.

Animals—22 racehorses without osteochondral injury and 37 racehorses with osteochondral injury.

Procedures—Horses without osteochondral injury were examined before and after 5 to 6 months of race training. Horses with osteochondral injury were undergoing arthroscopic surgery for removal of osteochondral fragments from carpal or metacarpophalangeal or metatarsophalangeal joints (fetlock joints). Serum, plasma, and fetlock or carpal synovial fluid samples were obtained and analyzed for SDF-1 concentration by use of an ELISA.

Results—In horses with fetlock or carpal joint injury, mean synovial fluid SDF-1 concentrations were significantly higher, serum SDF-1 concentrations were significantly lower, and synovial fluid-to-serum SDF-1 ratios were significantly higher than in untrained and trained horses. Synovial fluid SDF-1 concentrations were not significantly different between trained and untrained horses. Plasma SDF-1 concentrations were not different among the 3 groups. Results obtained with serum, compared with synovial fluid and plasma, had better sensitivity for differentiation between osteochondral-injured horses and uninjured horses. In horses with fetlock joint osteochondral injury, serum SDF-1 concentrations were correlated with radiographic and arthroscopic inflammation scores, but not arthroscopic cartilage scores.

Conclusions and Clinical Relevance—Results suggested that serum SDF-1 concentrations were more sensitive than plasma and synovial fluid concentrations for detection of osteochondral injury in the fetlock or carpal joint of racehorses. Analysis of serum and synovial SDF-1 concentrations in horses with experimentally induced joint injury may help define the onset and progression of post-traumatic osteoarthritis and aid in the evaluation of anti-inflammatory treatments. (Am J Vet Res 2014;75:722–730)