Vitamin D-dependent rickets type 2 in a four-month-old cat

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Vitamin D-dependent rickets type 2 is a group of disorders characterized by target organ resistance to calcitriol (1,25-dihydroxycholecalciferol).

Vitamin D-dependent rickets type 2 is characterized by hypocalcemia, secondary hyperparathyroidism, high plasma calcitriol concentrations, and clinical signs of rickets.

Treatment of vitamin D-dependent rickets type 2 consists of administration of calcitriol at a high dosage, particularly during growth periods; oral supplementation with calcium may also be required.

A 4-month-old male domestic shorthair cat weighing 2.5 kg (5.5 lb) was examined because of vomiting, diarrhea, muscle tremors, and mydriasis of approximately 18 hours’ duration. According to the owner, the cat had appeared healthy earlier that day. The cat was housed strictly indoors, was current on all vaccinations, and was fed a commercial dry food formulated for kittens.

On physical examination, the cat was alert and aware, but agitated, and had leg tremors when it walked. Rectal temperature was 39.1°C (102.4°F), and pulse rate was 260 beats/min, and respiratory rate was 32 breaths/min. Capillary refill time was 1 to 2 seconds, mucous membranes were pink, and pulses were strong and regular. No cardiac or pulmonary abnormalities were auscultated. On ophthalmologic examination, the pupils appeared mydriatic with a sluggish response to light; central opacities were present in both lenses. Results of a direct fundic examination were unremarkable, as were results of a neurologic examination.

Initial laboratory testing consisted of a CBC; measurement of PCV and plasma protein concentration; and measurement of serum glucose, urea nitrogen, creatinine, lipase, albumin, total calcium, sodium, potassium, and chloride concentrations and serum alanine aminotransferase and alkaline phosphatase activities. A urinalysis and fecal examination were also performed. Abnormalities consisted of mild hyperphosphatemia (7.4 mg/dL; reference range, 3 to 6 mg/dL) and marked hypocalcemia (3.9 mg/dL; reference range, 7.9 to 11.3 mg/dL) with a normal albumin concentration (3.4 g/dL; reference range, 2.3 to 3.9 g/dL).

Possible causes of the mild hyperphosphatemia that were considered included hemolysis, hypersomatropism, hypoparathyroidism, and soft-tissue trauma. Possible causes of the marked hypocalcemia that were considered included primary hypoparathyroidism, nutritional secondary hyperparathyroidism, hypomagnesemia, malabsorption-malassimilation, acute pancreatitis, and toxicoses. Electrocardiography was performed to determine the cause of the tachycardia. Findings consisted of sinus tachycardia with slight prolongation of the QT interval consistent with hypocalcemia.

Initial treatment consisted of infusion of lactated Ringer’s solution (2.5 mL/kg/h [1.1 mL/lb/h], IV). In addition, 10% calcium gluconate (1.0 mL/kg [0.45 mL/lb]) was administered slowly IV. An electrocardiogram was monitored continuously during administration of calcium gluconate, and no arrhythmias were seen. The muscle tremors were substantially less frequent following completion of this infusion, and serum total calcium concentration had increased to 4.1 mg/dL. At this time, a constant rate infusion of saline (0.9% NaCl) solution supplemented with 2.3 mL (4 mg) of 10% calcium gluconate, for a dose of 10 mg/kg/h (4.5 mg/lb/h), was begun at a rate of 6 mL/h and continued for 8 hours. This infusion provided a total of 200 mg of elemental calcium. Serum calcium concentration was monitored every 2 hours during the infusion.

A recheck ophthalmic examination by a board-certified veterinary ophthalmologist indicated that the bilateral central opacities in both lenses were nonvascular remnants of the hyaloid artery, causing small, stationary posterior polar cataracts. No other abnormalities were detected. The ophthalmologist thought that the mydriasis was most likely attributable to high sympathetic tone. Because the cataracts involved the lens capsule and not the lens itself, this helped to decrease the likelihood of primary hypoparathyroidism as a possible cause.

Possible causes of the hypocalcemia and hyperphosphatemia that were considered at this time included nutritional secondary hyperparathyroidism, osteomalacia, hyperthyroidism, hypomagnesemia, primary hypoparathyroidism, and rickets. Radiographs of the thorax and abdomen were obtained, and density of the bones and physes, as assessed by a board-certified radiologist, was considered to be normal, making nutritional secondary hyperparathyroidism and osteomalacia unlikely causes of the hypocalcemia and hyperphosphatemia in this cat. Serum that had been obtained when the cat was first examined, prior to any treatment, was tested for magnesium and total serum thyroxine (T4) concentrations. The magnesium concentration was slightly low (1.5 mg/dL; reference range, 1.9 to 2.6 mg/dL), but this degree of hypomag-
neumia was not considered sufficient to cause any of the clinical signs commonly associated with hypomagnesemia or to interfere with parathyroid hormone production, as can be seen with severe hypomagnesemia.\(^3\)\(^4\)

Total serum T4 concentration was in the reference range (1.8 µg/dL; reference range, 0.8 to 2.0 µg/dL). Samples of the serum were submitted to an endocrinology laboratory for determination of intact parathormone and ionized calcium concentrations. The intact parathormone concentration was high (19 pmol/L; reference range, 0 to 4 pmol/L), and the ionized calcium concentration was low (0.6 mmol/L; reference range, 1.0 to 1.4 mmol/L), ruling out hypoparathyroidism as the cause of the cat's problems.

On the basis of these results, a diagnosis of a vitamin D anomaly was made. To differentiate between vitamin D deficiency and the 2 types of vitamin D-dependent rickets, plasma calcitriol (1,25-dihydroxycholecalciferol) concentration was measured by using a sample obtained the day after admission. The plasma calcitriol concentration was high (61 pg/mL; reference range, 17 to 25 pg/mL), which is not consistent with vitamin D deficiency or vitamin D-dependent rickets type 1, but is consistent with vitamin D-dependent rickets type 2. With vitamin D-dependent rickets type 2, a high plasma calcitriol concentration is expected secondary to malfunction of vitamin D receptors essential to feedback control of calcitriol concentrations.

Treatment consisted of oral supplementation with calcium lactate (500 mg, PO, q 24 h)\(^5\) and calcitriol (125 ng, PO, q 24 h).\(^6\) A high dosage of calcitriol (approx 50 ng/kg [22.7 ng/lb]) was used initially to supersaturate the vitamin D receptors and, potentially, compensate for impaired binding of calcitriol, 1 of the common defects in vitamin D-dependent rickets type 2.\(^7\) The recommended dosage of calcitriol to compensate for deficient calcitriol production in dogs and cats with chronic renal failure is 2.5 to 3.5 ng/kg (1.1 to 1.6 ng/lb), PO, every 24 hours, and the maintenance dosage of calcitriol in dogs and cats with hypoparathyroidism is 5 to 15 ng/kg (2.3 to 6.8 ng/lb), PO, every 24 hours.\(^8\) The cat was discharged from the hospital on day 3.

The cat was reexamined 3 days later. No signs of hypocalcemia were noted during a physical examination, and the owner reported that the cat was acting normal at home. However, serum total calcium concentration was still low (5.8 mg/dL). Therefore, the owner was instructed to continue to administer calcium lactate and calcitriol at the same dosages in an attempt to see whether a longer duration of calcitriol administration would result in a greater calcium response. Four days later, the cat was reexamined again, and although results of a physical examination were normal and the owner reported no problems, the serum total calcium concentration was lower (5.4 mg/dL). Dosages of calcium lactate and calcitriol were increased to 1,000 mg, PO, every 24 hours and 250 ng, PO, every 24 hours, respectively. Eleven days later, serum total calcium concentration had increased (6.9 mg/dL) but was still less than the lower reference limit. Therefore, the medications were continued at the same dosages.

Two weeks later (4 weeks after the initial diagnosis), serum total calcium was within reference limits (8.9 mg/dL). Physical examination revealed that all permanent teeth had erupted, and the cat's size was considered to be appropriate for its age. No changes were made in the medication at this time.

Eleven weeks after the initial diagnosis, the cat was reexamined. The owner reported no problems, and results of a physical examination were unremarkable. Serum total calcium concentration was 10.9 mg/dL, and the dosage of calcium lactate was decreased to 500 mg, PO, every 24 hours. The calcitriol dosage was maintained at 250 ng, PO, every 24 hours. Five months after the initial diagnosis, the cat's serum total calcium concentration remained unchanged, and the owner elected to discontinue treatment with calcitriol for financial reasons. Thirteen months after the initial diagnosis, the cat was again reexamined. The owner reported that the cat had not had any problems in the intervening period, and serum total calcium concentration was 10.2 mg/dL. We believed that the cat had likely outgrown its high calcium requirement and that endogenous vitamin D production should have been adequate for normal calcium homeostasis at this time. Therefore, treatment with calcium lactate was discontinued at this time. The owner reported by telephone 6 months later that the cat was doing well and had not had any other problems.

Calcitriol is formed from the metabolism of cholecalciferol ingested in the diet or synthesized in the epidermis from 7-dehydrocholesterol. The skin of cats and dogs, however, contains only small quantities of 7-dehydrocholesterol, which does not permit adequate synthesis of cholecalciferol; therefore, dogs and cats are dependent on their diet as a source of calcitriol precursors. The primary biological action of calcitriol is to increase absorption of calcium from the intestines, thereby maintaining an adequate concentration in the body. The major target for calcitriol is the nucleus of newly formed and not yet differentiated intestinal cells; calcitriol appears to have no appreciable effects on calcium absorption of fully differentiated intestinal cells. The capacity for intestinal cells to absorb calcium is a direct function of the amount of vitamin D-dependent proteins, such as calcium-binding protein (calbindin), in those cells.\(^7\) Calcitriol is also required for normal bone mineralization during skeletal growth, and in the kidney, it is believed to stimulate retention of calcium and phosphorus by increasing proximal tubular reabsorption. Vitamin D receptors have also been found in numerous other cells, ranging from skeletal muscle to immune cells.\(^7\)

Rickets was first recognized in humans and reported as a clinical entity in 1550.\(^9\) It is seen primarily in children and is characterized by bowed weak legs, knuckle-like projections along the costochondral junctions, and deformities of the pelvis. In humans, 4 forms of rickets have been identified. The first is nutritional rickets resulting from a dietary vitamin D or phosphorus deficiency, the second is hereditary X-linked hypophosphatemic rickets, the third is vitamin D-dependent rickets type 1, and the fourth is vitamin D-dependent rickets type 2. Vitamin D-dependent rickets...
Vitamin D receptors. To our knowledge, vitamin D-dependent rickets type 2 in a cat has not been reported previously. Although a previous report described signs potentially compatible with vitamin D-dependent rickets type 2 in 2 cats, the cats were subsequently suspected to have metaphyseal chondrodysplasia.

The hyperphosphatemia observed in the cat described in the present report suggested that it did not have X-linked hypophosphatemic rickets or a nutritional phosphorus deficiency. Vitamin D-dependent rickets type 1 is a result of a deficiency in calcitriol production by the renal 1α-hydroxylase enzyme system and is associated with low to unmeasurable plasma calcitriol concentrations, whereas this cat had a high plasma calcitriol concentration. By contrast, because functional vitamin D receptors in the kidney are required for feedback suppression of calcitriol synthesis, the gene defect associated with vitamin D-dependent rickets type 2 results in high plasma calcitriol concentrations, as seen in this cat.

Vitamin D-dependent rickets type 2 is a group of disorders characterized by target organ resistance to calcitriol. In some patients, the defect is associated with inefficient binding of calcitriol by vitamin D receptors. In these patients, the defect can be compensated for by administered calcitriol at high dosages, as was the case in the cat described in the present report. In other patients, the defect is associated with impaired binding by the vitamin D receptors and cannot be compensated for by administering high dosages of calcitriol. This defect is much more likely to be fatal either in utero or in early postpartum life.

Vitamin D-dependent rickets type 2 is characterized by hypocalcemia, secondary hyperparathyroidism, high plasma calcitriol concentrations, and clinical signs of rickets. The cat described in the present report had a mild clinical form of vitamin D-dependent rickets type 2. Thus, there most likely was only modest impairment of binding of calcitriol to the cat’s vitamin D receptors. This cat had clinical signs associated with the hypocalcemia, but no radiographic changes associated with rickets. In addition, endocrinology testing revealed marked increases in serum parathormone and plasma calcitriol concentrations, which is consistent with findings in humans. In human patients, function of the vitamin D receptors can be tested by culturing skin fibroblasts and measuring activity and binding capacity of the receptors. In 1 study, affected human patients, the activity of the vitamin D receptor, when stimulated with a standard concentration of calcitriol, ranged from 50 to 82% of the activity of receptors in unaffected controls, and binding capacity of the nucleus for calcitriol was 7 to 27% of binding capacity for unaffected control patients. This study also showed that vitamin D-dependent rickets type 2 is an autosomal recessive disease in humans. It is reasonable to conclude that a similar inheritance pattern would be true for veterinary patients.

Treatment of vitamin D-dependent rickets type 2 in people consists of administration of high dosages of calcitriol, particularly during growth periods. Treatment is typically lifelong; however, some human patients require only mineral supplementation. The cat described in the present report was given high dosages of calcitriol and calcium lactate during the rapid growth phase. The dosage of calcitriol slowly decreased as the cat’s weight increased, until supplementation was finally discontinued. Calcium supplementation was also eventually discontinued without any apparent adverse effects.

References


Animal Health Diagnostic Laboratory, Michigan State University, East Lansing, Mich.