Apparent Resolution of Canine Primary Hypoparathyroidism with Immunosuppressive Treatment

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A 1-year-old, male intact, miniature poodle was presented as an emergency referral to the Queen's Veterinary School Hospital, University of Cambridge, with 24 hours of inappetence and lethargy, followed by acute collapse, seizures, and muscle twitching. The clinical onset was 3 weeks after routine (first) annual vaccination; the dog had no history of other drug or toxin exposure.

On presentation, the dog showed weakness, muscular twitching, and tetany. The dog also had petechiation of the hard palate and oral mucosa, and lingual bleeding. The referring veterinarian reported hyperthermia (40.5°C, 105°F), but body temperature had decreased by the time the dog reached the hospital because the referring veterinarian had induced cooling with wet towels; temperature on arrival at QVSH was 36.3°C (97.3°F). Body condition was normal (4/9) at presentation with a weight of 7.6 kg.

Serum biochemistry disclosed total hypocalcemia (5.32 mg/dL; reference range, 8.6–11.8; 1.33 mmol/L, reference range, 2.15–2.95) and hyperphosphatemia (7.03 mg/dL, reference range, 2.91–6.59; 2.27 mmol/L, reference range, 0.94–2.13). Azotemia was detected, with serum urea concentration of 60.8 mg/dL (reference range, 7.0–24.9; 21.7 mmol/L, reference range, 2.5–8.9) and creatinine concentration of 1.98 mg/dL (reference range, 0.3–1.4; 175 μmol/L, reference range, 27–124); these reduced within 24 hours after IV crystalloid fluid therapy,[a] with serum creatinine concentration normalizing (1.44 mg/dL, reference range, 0.38–1.54; 127 μmol/L, reference range 34–136), suggesting a prerenal azotemia. Muscle enzyme activities also were found to be increased, with CK > 2,000 IU/L (reference range, 42–206), AST > 1,000 IU/L (reference range, 12–49), and ALT 901 IU/L (reference range, 14–67); these increases in nonspecific markers of muscle injury were

Abbreviations:

ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
CK	creatine kinase
ECF	extracellular fluid
ELISA	enzyme-linked immunosorbent assay
IMT	immune-mediated thrombocytopenia
IVFT	intravenous fluid therapy
MRI	magnetic resonance imaging
OSPT	one stage prothrombin time
PTH	parathyroid hormone
QVSH	Queen's Veterinary School Hospital

considered likely to be secondary to the seizures and tetany. Muscle disease was not otherwise investigated.

Hematology disclosed severe thrombocytopenia (7×10^9 cells/L reference range, 175–500), which was confirmed by blood film examination. Coagulation times were normal (OSPT 9.1 seconds reference range, 7.6–11.6; APTT 14.3 seconds reference range, 12.5–25). Urine sediment examination showed no abnormalities.

While awaiting results of serum parathyroid hormone (PTH) measurement, hypocalcemia was treated with IV calcium gluconate[b] (50 mg/kg IV over 20 minutes, as required) followed by a high initial dose of alfacalcidol (0.06 μg/kg PO q12h),[c] and calcium carbonate (15 mg/kg elemental calcium PO q12h)[d] after acute clinical signs resolved. Immunosuppressive dosages of prednisolone (2.5 mg/kg PO q24h)[e] and cyclosporine (4 mg/kg PO q24h)[f] were prescribed for suspected immune-mediated thrombocytopenia (IMT). The thrombocytopenia was not extensively investigated, but considering its severity, IMT was considered the most likely cause. Infectious causes of thrombocytopenia are uncommon in the United Kingdom, and the dog had no history of tick exposure nor had it lived in or traveled to an area where *Anaplasma phagocytophilum* was prevalent; *Ehrlichia platys* does not occur in the United Kingdom, and *Angiostrongylus vasorum* infection was considered unlikely given that the dog did not show any respiratory signs or abnormalities on thoracic radiographs. Platelet count increased to 178×10^9 cells/L within 8 days and this rapid response to treatment provided further support for the suspected diagnosis of IMT. Thoracic radiographs and abdominal ultrasound examination were normal. Because no precipitating factors were found on screening medical testing, the diagnosis of suspected primary (idiopathic) IMT was made.

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Over the 48 hours after admission, 5 IV boluses of 100 mg/kg calcium gluconate (5% solution) were administered, but an IV infusion (5% solution) was necessary to control clinical signs (10–15 mg/kg/h initially, but variable depending on serum calcium concentration and clinical signs). The infusion was maintained, gradually decreasing over 72 hours.

Concurrent with hypocalcemia (serum ionized calcium concentration 2.88 mg/dL; 0.72 mmol/L), serum PTH concentration was <10 pg/mL (reference range, 20–65), confirming a diagnosis of hypoparathyroidism. Because no precipitating factors were found on screening medical testing, the diagnosis of primary (idiopathic) hypoparathyroidism was made. Parathyroid hormone measurement was performed by an ELISA technique validated in dogs,[g] and the sample was carefully processed, including immediate separation of plasma and freezing before shipping to the laboratory,[h] which confirmed that the sample arrived in suitable condition (ie, frozen).

Despite resolution of overt clinical signs, hypocalcemia remained until the 18th day of hospitalization. Magnesium measurement was undertaken owing to failure of treatment to normalize serum calcium concentration after a week of treatment. Serum total magnesium concentration was within the reference interval (1.38 mEq/L reference range, 1.30–2.04; 0.69 mmol/L, reference range, 0.64–1.02) with concurrent hypocalcemia (ionized 2.8 mg/dL; 0.7 mmol/L). The prednisolone dose was tapered, and prednisolone was stopped after 12 days of treatment because of concern that hypercalciuria was preventing adequate control of the hypocalcemia.

Extravasation of calcium gluconate during the initial emergency treatment caused extensive skin necrosis of the right hindlimb. This complication was successfully treated with repeated surgical debridement, wound dressing, antibiotics, pain relief and when appropriate, surgical wound closure, over the next 4 weeks.

Three days after cessation of prednisolone, serum ionized hypercalcemia (6.4 mg/dL; reference range, 4.72–5.6; 1.6 mmol/L, reference range, 1.18–1.4) developed. Alfacalcidol was decreased (0.02 μg/kg PO q12h, and subsequently 0.01 μg/kg PO q12h) and calcium carbonate was stopped. Alfacalcidol was stopped after a further week of worsening hypercalcemia despite the lower dosage. Tests of renal function (serum urea and creatinine concentrations) were normal throughout this period.

The dog was discharged after 4 weeks, once the hindlimb wound had been closed. At discharge, the dog was receiving only cyclosporine (5 mg/kg PO q24h), meloxicam (0.1 mg/kg PO q24h),[i] and co-amoxicillin clavulanate (18 mg/kg PO q12h).[j] The dog's serum ionized calcium concentration at discharge was 5.64 mg/dL (1.41 mmol/L). Three days after discharge, the ionized calcium concentration was 4.92 mg/dL (1.23 mmol/L). With the intent of avoiding hypocalcemia, the alfacalcidol was restarted (0.02 μg/kg PO q12h), but doing so once again led to hypercalcemia 6.4 mg/dL (1.6 mmol/L) within 1 week, and supplementation was stopped.

Despite no further treatment with calcium supplementation or alfacalcidol treatment, over the next 12 months clinical signs did not recur, and monthly measurements have confirmed continued normocalcemia (serum ionized calcium concentration ranging between 5.52 and 5.64 mg/dL (1.38 and 1.41 mmol/L). Over the months after discharge, the dog gained a substantial amount of weight. The weight-adjusted cyclosporine dosage decreased to 2.5 mg/kg PO q24h over 3 months, whereas the total dose administered was not altered. The dosage was then tapered over the next 6 months to 1 mg/kg PO q24h followed by q48h before stopping. At the time of writing, the dog had not received cyclosporine for 6 months, with continued stable serum calcium concentrations and no recurrence of clinical signs. Hematology also was normal.

Because of apparent resolution of the hypoparathyroidism, serum PTH concentration was measured after 3 months and was within reference range (61 pg/mL; reference range, 20–65; concurrent serum ionized calcium concentration: 5.56 mg/dL, 1.39 mmol/L).

Calcium regulation is vital for normal physiology, with roles in muscle contraction, neuronal activity and other cellular functions such as exocytosis and enzyme activation. The dog's clinical signs all can be explained by the documented hypocalcemia; the mucosal petechiation likely was because of the thrombocytopenia, but may also be related to hypocalcemia because calcium is required for normal platelet function and the coagulation cascade. Although the main store of calcium in the body is the skeletal system, the most important control point is the concentration of calcium in the extracellular fluid (ECF) pool. Regulation of the ECF calcium depends on movement between the ECF and 3 organs: bone, gastrointestinal tract, and kidneys. The parathyroid glands provide the main control of calcium and phosphate, by producing parathyroid hormone (PTH) with effects of increasing calcium and decreasing phosphate concentrations in the ECF pool. The parathyroid gland responds directly to extracellular calcium concentrations, and therefore the concurrent finding of low serum calcium concentration and undetectable PTH confirms the inappropriate response of the parathyroid glands to hypocalcaemia, which characterizes hypoparathyroidism.[1]

Potential causes of hypoparathyroidism, which have been previously reported in dogs, are listed in Table 1. In this case, the diagnosis of primary hypoparathyroidism was reached due the combination of low serum total and ionized calcium concentrations, high serum phosphate concentration, undetectable PTH, normal renal function, and a lack of any other causes.[2] Renal function was considered normal because of the rapid resolution of azotemia with IVFT, indicating prerenal azotemia. The dog had no history of trauma, surgery, or drug administration (aside from vaccination). Magnesium deficiency is uncommon in healthy dogs, but incidence is much higher in the critical care setting, with reports of up to 54% of dogs in intensive care having low serum magnesium concentrations at admission.[3]

Table 1.   Causes of hypoparathyroidism in dogs.

Primary/idiopathic
Suspected Immune mediated
Absence/destruction of parathyroid glands
Thyroidectomy
Other neck surgery
Severe soft tissue injury
Radiation damage
Magnesium deficiency/excess
Sudden reversal of chronic hypercalcaemia
Tumor lysis/removal
Parathyroidectomy (treatment of hyperparathyroidism)
Other causes (reported only in humans)
Drug induced—chemotherapeutics (asparaginase,
doxorubicin, cytosine arabinoside), cimetidine,
aluminum, ethanol
Genetic/hereditary agenesis of the parathyroid glands
(eg, DiGeorge Syndrome/22q11 deletion)
Deposition of minerals—eg, Copper in Wilson's
Syndrome[22] & Iron in Hemochromatosis[23]

Adapted from Kirk's Current Veterinary Therapy XIV.[2]

Hypomagnesemia can cause both disorders of PTH production and end organ resistance to PTH.[4]

The optimal method for measuring magnesium concentration has not been established, and it is possible to have normal serum total magnesium concentration despite a total body magnesium deficit because of the intracellular location of 99% of the body's magnesium.[5] In this case, magnesium concentration was not measured until day 7 after admission, and only serum total magnesium concentration was measured. Ionized magnesium concentration may have provided additional information, and the possibility that the dog was suffering from a magnesium deficit cannot be excluded by the single magnesium measurement available. However, hypomagnesemia is unlikely to have been the cause of the hypoparathyroidism in this dog because it would only be expected to have this effect if it were severe; mild hypomagnesemia actually increases PTH secretion.[6] In addition, the hypocalcemia remained for 10 days after documentation of a normal serum magnesium concentration. To the authors' knowledge, the speed of recovery of calcium concentration with magnesium supplementation in hypocalcemic, hypomagnesemic dogs has not been documented, but it would be expected to be rapid. In humans, PTH recovery occurred within 1 minute of magnesium infusion, and calcium normalized after approximately 4 days.[4]

Canine primary hypoparathyroidism is an idiopathic condition thought to be caused by immune-mediated lymphocytic parathyroiditis and destruction of the parathyroid gland.[7] Although no consensus has been reached on optimal management, it requires lifelong treatment with vitamin D analogs with or without calcium supplementation.[2]

Some cases of canine hypoparathyroidism may resolve, but reports in the veterinary literature are limited to cases induced by temporary damage to or suppression of the parathyroid glands, such as those caused by magnesium deficiency, trauma or iatrogenically by thyroidectomy[8] or after treatment of hypercalcemia after parathyroidectomy[9] or treatment of a malignancy.[10]

To the authors' knowledge, this is the first reported case of naturally occurring canine primary hypoparathyroidism to resolve without lifelong vitamin D and calcium supplementation. Conventional management does not include immunosuppressive treatment, but this approach was used because of the concurrent occurrence of IMT. To the authors' knowledge, there are no reports of the use of immunosuppressive treatment in dogs with primary hypoparathyroidism.

In humans, there are occasional reports of other causes of hypoparathyroidism resolving. Alcohol consumption is a reported trigger for hypoparathyroidism, and moderate alcohol consumption caused transient but clinically unimportant hypoparathyroidism in human volunteers.[11] In 1 case report, a person who developed transient hypoparathyroidism, thought to be secondary to pyrexia, experienced resolution after correction of body temperature.[12]

In the medical literature, there is a single case report of resolution of primary hypoparathyroidism in a human patient, in whom hypoparathyroidism spontaneously resolved after 2 years of treatment with vitamin D analogs and calcium supplementation; the cause of resolution was unknown.[13]

The role of vaccination in this dog is unknown. Vaccinations have been linked to the occurrence of immune-mediated diseases, but adequately powered studies are lacking to prove causation in dogs. A recent study designed to investigate the link between vaccination and immune-mediated thrombocytopenia failed to demonstrate increased risk in affected dogs, although this study likely was underpowered.[14] In humans, recent vaccination has been implicated in the development of several autoimmune conditions, but the evidence is only considered strong in a few conditions, including IMT, arthritis, diabetes mellitus, Guillain Barré syndrome (polyradiculoneuritis), and transverse myelitis.[15] To the authors' knowledge, hypoparathyroidism has not been reported to be associated with vaccination in humans or dogs.

The possibility remains that the hypoparathyroidism was transient or self-resolving, potentially related to critical illness and pyrexia. In humans, hypocalcemia is documented commonly during sepsis, but the mechanism of its development has not been definitively established. In many cases, PTH concentrations are appropriately increased.[16] In a small number of cases, concurrent hypocalcemia and hypoparathyroidism are detected, but the finding of an extremely low PTH concentration, rather than a relative, inappropriate hypoparathyroidism was rare.[17] These changes are related to proinflammatory cytokines, particularly IL-6 and IL-1β, which lead to increased transcription of the calcium-sensing receptor and a lowered calcium set point.[18] Hypoparathyroidism related to sepsis has not been documented in dogs. In this dog, it seems unlikely that the hypoparathyroidism was related to a state of sepsis

because the dog's clinical signs all could be explained by the hypocalcemia, and were not consistent with sepsis. Furthermore, the hypocalcemia did not resolve without intense intervention over the following 3 weeks, and despite resolution of the dog's thrombocytopenia within a much shorter period. Also, the severity of the hypoparathyroidism was more extreme than is seen in humans, where relative hypoparathyroidism is more commonly recorded.

A final plausible explanation for the transient nature of the disease would be parathyroid hemorrhage, secondary to the IMT. In addition to a lack of previous reports, it is unlikely that hemorrhage would affect sufficient parathyroid tissue to have a clinically relevant effect on parathyroid function, given the presence of 4 parathyroid glands, located at the poles of the thyroid glands, without other concurrent clinical signs.

Given the apparent successful use of immunosuppressive treatment in a suspected immune-mediated condition, it is possible that this treatment was responsible for the response seen. Both prednisolone and cyclosporine were used in the management of the case. Although it is possible that prednisolone contributed to the response, the short treatment time and apparent clinical resolution after the cessation of prednisolone treatment, makes it more likely that cyclosporine contributed to resolution. Cyclosporine is a naturally occurring fungal compound with profound immunosuppressive properties. Its main activity is to inhibit T-cells by inhibition of calcineurin, preventing activation of T-helper cells and the production of IL-2, which in turn prevents clonal expansion of T-cells, particularly CD8 + cytotoxic T-cells.[19] Its use is licensed for dogs with atopic dermatitis, and it has been used in other immune-mediated conditions,[20] but not in hypoparathyroidism. Aside from the immunosuppressive effects of cyclosporine, it is known to affect calcium and parathyroid metabolism in humans and dogs. A study of dogs with atopic dermatitis showed that, while calcium concentrations were only mildly affected, treatment with cyclosporine increased PTH concentrations.[21] The clinical relevance of this effect in the dog of this case report is questionable given that in atopic dogs the parathyroid gland would be functioning normally, whereas here the concurrent undetectable PTH and profound hypocalcemia indicated parathyroid gland failure. The effects on PTH concentrations are complex owing to cyclosporine's ability to increase urinary calcium excretion in some animals.

The main limitation of this case report is the lack of histopathology to confirm lymphocyte-mediated destruction of the parathyroid glands, but biopsy of the parathyroid gland is not normally indicated in the management of primary hypoparathyroidism in the dog. In retrospect, additional imaging of the parathyroid glands with ultrasound or MRI would have been desirable, but were not considered necessary at the time of initial diagnosis. The unique nature of the case only became apparent over the subsequent months. Whether or not treatment was responsible for resolution, this report still represents a unique finding of transient primary hypoparathyroidism.

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