CLINICAL REPORT

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Primary hypoparathyroidism in a dog: a case report

Hipoparatireoidismo primário em cão: relato de caso

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ABSTRACT: Primary hypoparathyroidism is a rare metabolic condition that can affect domestic animals. The resulting hypocalcemia and hyperphosphatemia can lead to neurological and respiratory changes, as well as cardiac arrhythmias. The aim of the present study is to report the occurrence of primary hypoparathyroidism in a dog and describe the clinical and diagnostic aspects. A 7-year-old male dog with convulsive seizures and spastic limb paralysis was attended to in the municipality of Resende-RJ. After previous therapy with no response to phenobarbital use, serum PTH and ionized calcium levels were measured, revealing a decrease in both. Therapeutic response was observed with the use of calcium gluconate and balancing of circulating potassium via ion channels. Clinical signs characterized by excitability, seizures, muscle fasciculations, and muscular tetany point to a thorough investigation of possible differential diagnoses of calcium disorders. Studies involving the etiological and pathophysiological mechanisms of primary hypoparathyroidism should be encouraged to suggest early therapeutic protocols.

KEYWORDS: Hypocalcemia; parathyroid; dog; convulsive seizures.

RESUMO: O hipoparatireoidismo primário é uma afecção metabólica rara que pode acometer os animais domésticos. A hipocalcemia e a hiperfosfatemia resultantes podem ocasionar alterações neurológicas e respiratórias, além de arritmias cardíacas. O objetivo do presente trabalho é reportar a ocorrência de hipoparatireoidismo primário em cão e relatar os aspectos clínicos e diagnóstico. Foi atendido, no município de Resende-RJ, um cão, macho de 7 anos de idade com crises convulsivas e paralisia espástica de membros. Após terapia prévia sem resposta ao uso de fenobarbital, foi realizada dosagem sérica de PTH e cálcio iônico, que revelou diminuição dos mesmos. Houve resposta terapêutica ao uso de gluconato de cálcio e equilibro de potássio circulante, via canais iônicos. Os sinais clínicos caracterizados por excitabilidade, convulsões, fasciculações musculares e tetania muscular, apontam para investigação criteriosa dos possíveis diagnósticos diferenciais dos distúrbios do cálcio. Estudos envolvendo os mecanismos etiológicos e fisiopatológicos do hipoparatireodismo primário devem ser estimulados, a fim de sugerir protocolos terapêuticos precoces.

PALAVRAS-CHAVE: Hipocalcemia; paratireoide; cão; crises convulsivas.

INTRODUCTION

Hypoparathyroidism is a rare calcium homeostasis disorder characterized by low or undetectable levels of parathyroid hormones (PTH) that progress to hypocalcemia and hyperphosphatemia (Winner, 2019; Wolf *et al.*, 2020) . This disorder can affect humans (Bilkizian, 2020), dogs (Kang *et al.*, 2009; Freitas *et al.*, 2014; Aléssio *et al.*, 2019), cats (Skelly, 2021), horses (Durie *et al.*, 2010), cattle (Villarroel *et al.*, 2013), and some wild species such as ferrets (Martinez *et al.*, 2015).

In dogs, hypoparathyroidism most frequently manifests as idiopathic primary hypoparathyroidism caused by immune-mediated destruction of the parathyroid gland, resulting from lymphocytic immune-mediated parathyroiditis or the replacement of normal glandular tissue with fibrous tissue.

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Other subtypes, such as iatrogenic hypoparathyroidism secondary to parathyroidectomy and pseudohypoparathyroidism, result from PTH resistance (Neves, 2020).

Hypoparathyroidism can manifest in dogs from the age of 6 weeks to 13 years; predisposition is related to sex, and females have a higher incidence. The most affected breeds are Toy Poodles, Miniature Schnauzers, Labrador Retrievers, German Shepherds, and Terriers (Serra *et al.*, 2010; Tuohy *et al.*, 2012).

The reported clinical signs attributed to hypocalcemia are more noticeable by their effects on the neuromuscular system including increased excitability, generalized convulsions, focused muscle contractions, cramps in the pelvic limbs and muzzles, tetany, ataxia, weakness, lethargy, inappetence, intense facial rubbing, tachypnea, tachycardia, bronchospasm, apnea, polyuria, and polydipsia(Rubin; Carr, 2007; Albuquerque *et al.*, 2015; Jaffey *et al.*, 2019; Ballocco *et al.*, 2021).

This case report addressed the laboratory findings and corroborated the clinical signs and success of the therapies used.

CASE REPORT

This report was authorized by the tutor, to use the data herein for academic and scientific purposes with a guarantee of anonymity, who signed the Free and Informed Consent Form.

In a private clinic in Resende, Rio de Janeiro, a 7-year-old male canine patient with beige fur who weighed 14 kg presented with mixed breed and an Body Condition Score5/9 (LAFLAMME, 1997), according to WSAVA Global Nutrition Guidelines. The patient had muscle contractions, tremors, tonic-clonic seizures, and spastic paralysis with moments of limb flexion(Video QR Code 1).

The dog was treated with phenobarbital (2mg/kg/BID), orally, but his clinical condition did not improve.Abdominal ultrasonography and radiography of the pelvic limb and chest were performed previously.. Ultrasonography revealed duodenitis, pancreatitis, hepatomegaly, and splenomegaly.

A chest radiograph revealed mild bronchial and interstitial patterns. Serum biochemistry indicated a significant increase in alanine aminotransferase 397 U/L (ref. 10 – 88 U/L) and non-reactivity to canine pancreatic lipase, using the Enzyme Linked Immuno Sorbent Assay (ELISA) test, specific to this enzyme (SNAP-cPL, IDEXX®).

The blood count and serum biochemistry showed mild leukocytosis 17.300 cel/mm^3 (ref. 6.000 a 17.000 cel/mm^3), monocytopenia 4 (ref. 150 a 1.350 cel/mm^3),, eosinopenia 0 (ref. 100 a 1.250 cel/mm^3),, hypertransaminasemia 162 UI/L (ref. 10 a 88 UI/L),, hyperaminotransaminase 397 UI/L (ref. 10 a 88 UI/L),, hyperlipasemia 232 UI/L (ref. 13 a 200 UI/L) and hyperamylasemia 1.412 UI/L (ref. 300 a 1200 UI/L).

Seven days after the first visit, the dog was sent for follow-up and presented with tetanic seizures, abdominal pain, tachypnea, and cramps (Video QR Code 2).

In addition, generalized tremors, a rigid gait, intense biting and licking of the paws, fasciculations, rubbing and facial itching, vomiting, and diarrhea were observed.

The clinical examination revealed a 38.3 °C body temperature (ref. 37,5°C – 39,2°C), 112 bpm heart rate (ref. 60-120 bpm), 84 rpm respiratory rate ref. 18 - 36 rpm), and 190 mmHg (ref. < 140 mmhg) systolic blood pressure measured using the doppler method.

Hematological tests indicated lymphopenia 636 cel/mm^3 (ref. 1.000 a 4.800 cel/mm^3), eosinopenia 0 (100 a 1.250 cel/mm^3),,7,4 g/dL(ref. 5,4 a 7,1g/dL), mild hyperalbuminemia 3,4 g/dL (ref. 2,6 a 3,3 g/dL), hypertransaminaemia 378 U/L (ref. 10 a 88 U/L),, mild hyperglycemia 122 mg/dL (ref. 60 a 120 mg/dL), hypocalcemia 4,0 mg/dL (ref. 8,0 a 12,0 mg/dL),, ionic calcium 0.67 mmol/L (ref.1,15 - 1,38 mmol/L).

Based on the results of serum biochemistry and evident hypocalcemia, initial intravenous therapy was administered with lactated Ringer's solution and calcium gluconate (0.5 mL/kg IV over 20 minutes).. Approximately 30 minutes after the calcium therapy, the dog developed mild fasciculations. Maintenance therapy with calcium gluconate alone was initiated after dosing with ionized calcium. However, even with calcium gluconate supplementation, the patient had clinical signs of tremors and agitation (Video QR code 3).

QR Code 1. 7-year-old canine patient with spastic paralysis, with flexion and extension of pelvic limbs (Source: authors' personal archive, 2022).

QR Code 2 . 7-year-old canine patient with discomfort in the nostril region, suggestive of focal cramps limbs (Source: authors' personal archive, 2022).

QR Code 3 . 7-year-old canine patient, with obvious agitation, tremors in the pelvic limbs and tachypnea (Source: authors' personal archive, 2022).

Another serum and follow-up measurement of ionized calcium 0.68 mmol/L (ref. 1,15 - 1,38 mmol/L) and magnesium 1.9 mg/dL (ref.1,7 -2,4 mg/dL) was required.

Due to the calcemic disorder observed in previous tests, serum parathyroid hormone and ionic calcium levels were measured using chemiluminescence to confirm the suspicion of hypoparathyroidism.

The results demonstrated significantly decreased serum concentrations of PTH 0.50 pmol/L (ref. 1,10 - 10,60 pmol/L) and ionized calcium 0.76 mmol/L (ref. 1,15 - 1,38 mmol/L),, and are compatible with primary hypoparathyroidism. The already established therapy was maintained with calcium gluconate 10% (0,5ml/kg/BID/IV), equivalent to 50 mg/kg IV for 20 minutes, which resulted in rapid remission of clinical signs as the days passed. Therapy with calcium gluconate 10% was instituted for 1 week and after the dog was discharged. Calcium carbonate (50 mg/kg/BID) and vitamin D (500 UI/kg/SID), were prescribed orally for 30 days.

The effects of intravenous calcium infusion persisted for 1–2 hours. Maintenance therapy was then instituted with oral vitamin D and calcium supplementation for 24–96 hours after the disappearance of clinical signs.

Two months after the initiation of this therapeutic approach, the patient recovered fully, and the clinical signs previously reported by the owners were not observed. The patient was healthy and had vital parameters without changes in the reviews, as well as blood pressure and hematological values; however, there were some serum biochemical changes such as an increase in alanine aminotransferase 136 UI (ref. 10 - 88 UI);, total protein 7,8 g/dL (ref.5,4 - 7,1 g/dL), and globulin levels 5,1g/dL (ref. 2,7 - 4,4 g/dL, although the total calcium value was 8.6 mg/dL 8,6 mg/dL (8 - 12 mg/dL).

DISCUSSION

The severity of clinical signs depends on the degree of hypocalcemia. Most animals do not manifest clinical signs until the total calcium concentration is less than 1.5 mmol/L and the ionized calcium content is below approximately 0.8 mmol/L (Skelly, 2015). These facts were evident in the clinical signs of this patient who presented with varying degrees of symptoms from slight tremors to convulsive episodes with cramps, muscle fasciculations, muscular tetany, and facial itching, in addition to hyperesthesia.

Hypocalcemia values also vary according to the acid-base balance in an animal because the presence of alkalosis reduces the ionized component and makes clinical signs more likely, which can be represented by tachypnea, and in an attempt to maintain homeostasis initially, alkalinization may occur through HCO3 ion saturation (Schenck *et al.*, 2006).

Most diseases that cause hypocalcemia are associated with mild to moderate hypocalcemia, whereas primary hypoparathyroidism and eclampsia are more likely to be due to severe hypocalcemia. Puerperal tetany, which occurs most frequently at 1–4 weeks after giving birth or in the final stage of pregnancy, is easily identified, and its diagnosis is relatively easy. Therefore, hypoparathyroidism is the most likely cause of symptomatic hypocalcemia in dogs and cats outside the puerperal period, such as the epidemiological application of the present report because the patient was male. Neuromuscular dysfunction is the most common clinical sign of hypocalcemia in dogs. The tremors and generalized tetanic seizures exhibited by the dog in this report are consistent with previously described signs of severe hypocalcemia (Feldman; Nelson, 2004; Schenck *et al.*, 2006; Wolf *et al.*, 2020).

In a retrospective study of hypocalcemic dogs, 71% of the patients had seizures and 65% had muscle fasciculations, tremors, tetany, cramps, and facial pruritus, which are believed to be associated with cramping of the masseter and temporalis muscles caused by hypocalcemia or may result from a "tingling" sensation around the mouth or distal extremities (Russel *et al.*, 2006). These reported data are consistent with those observed during clinical care in this patient, who presented with intense discomfort, behavioral changes, and snout manipulation with the thoracic paws, in addition to episodes of muscular rigidity and decubitus.

Hyperthermia due to excess neuromuscular activity has been observed in 35% of patients (Russel *et al.*, 2006; Wolf*et al.*, 2020), however this clinical sign was not observed in the dog in this study. Other typical signs include behavioral changes in 53% of patients such as ataxia, vocalization, agitation, and incoordination; abdominal pain in 24%; hyperventilation in 47%; and anxiety or acute pain associated with tetany that can worsen metabolic alkalosis, which is possibly one of the factors that caused very low values for the patient in this case. Humans with hypoparathyroidism humans (and presumably dogs) may hyperventilate episodically and secrete increased amounts of epinephrine; hyperventilation in healthy people can decrease serum iCa concentrations (Wolf *et al.*, 2020).

Comorbidities involving the digestive tract can induce hypocalcemia because of reduced calcium absorption leading to diarrhea due to increased peristalsis. Thus, diarrhea in

hypocalcemic patients, whether caused by a primary disorder of the digestive tract or secondary to hypocalcemia, is a frequent finding (Rubin; Carr, 2007). The mechanism responsible for abdominal pain is unknown, although it may be the result of increased gastrointestinal motility or spasm and/or increased excitability of nervous tissue, which further highlights the episodes of vocalization and abdominal rigidity on palpation, as were present in the dog in this report.

After triggering compensatory mechanisms of the circulatory system, the two main clinical signs in this patient were systemic arterial hypertension, possibly resulting from the inactivity of calcium channels in the vascular endothelial walls, and epinephrine release, which favors intense vasoconstriction and impacts increased pressure, as verified during assessment. Furthermore, tachypnea possibly triggers the initial control of acid-base balance and favors an intense reduction in the circulating calcium ion levels, which worsens the condition. Owing to the progressive reduction in the concentration of extracellular calcium, both central nervous system and peripheral nerves become more excitable, and signs may progress to seizures and generalized tetany (Feldman; Nelson, 2004). Clinical sign severities are determined by the magnitude of hypocalcemia, as well as the duration and rapidity of onset. Tetany is likely to be present when total calcium decreases to <1.25 mmol/ or iCa <0.7 mmol/L.

Notably, there are possible differential diagnoses of hypoparathyroidism resulting from hypocalcemia, since this condition should not be the first to be considered in a clinical routine because others such as chronic kidney disease, acute kidney injury, urinary tract obstruction, hypomagnesemia, hypoalbuminemia, puerperal tetany (in females), diabetes mellitus, intestinal malabsorption syndromes, nutritional secondary hyperparathyroidism, anticonvulsant therapy, ethylene glycol poisoning, phosphate-containing enema, vitamin D deficiency, medullary thyroid carcinoma, tumor lysis and chemotherapy quimioterapia (Cardoso, 2015; Martínez *et al*., 2015) are more frequent. All of these were ruled out in the current patient with the exception of acute pancreatitis, which, although had normal values from the rapid test, can occur in cases of false negatives, although with the other findings and interpretations as the case progressed, was ruled out.

Changes in blood count and serum biochemistry were observed, and the biochemical results revealed an increase in glucose, total protein, albumin, ALT, alkaline phosphatase, and gammaglutamyltransferase. The increase in gamma-glutamyltransferase in the dog in this report was due to phenobarbital use (Ettinger; Feldman, 2004). Anticonvulsants are known to cause hypocalcemia, which can mask the underlying condition. However, the clinical signs presented by this dog occurred prior to phenobarbital use and, this combined with the normality of the ultrasound findings, indicated a significant increase in liver enzymes. An increase in these enzyme levels has been reported in dogs with hypoparathyroidism following prolonged anticonvulsant use (Fernandez; Kidney, 2007). A review of nine primary hypoparathyroidism cat cases revealed that 1/3 had elevated serum ALT levels of an unknown origin (Barber, 2004). Another possibility is that this increase is associated with seizures and tetany (Warland *et al*., 2015).

Neuromuscular changes can cause hypoglycemia due to oxygen demand and consequent energy expenditure; however, hypoglycemia was not an abnormality found in this patient, possibly compensated by immediate reserves through the glycolytic pathways. In dogs with hypocalcemia, a reduction in serum albumin levels causes a decrease in the fraction of circulating calcium bound to proteins. Increased total protein and albumin levels are uncommon in dogs with hypoparathyroidism, whereas reductions in total protein and/or albumin concentrations are generally observed. In this dog, we attributed the increase in total protein and albumin levels to dehydration, vomiting, and diarrhea, with a loss of this circulating component (Barber, 2004).

Changes such as leukocytosis, leukopenia, eosinopenia, and monocytosis were regarded as related to the stress leukogram, as these findings are not common in animals with hypocalcemia and hypoparathyroidism; however, another explanation for these abnormalities was a diagnosis of canine monocytotropic ehrlichiosis and hematuria resulting from prostate hyperplasia, which were also observed in this dog during the hospitalization period (Fernandez; Kidney, 2007).

The diagnosis of hypoparathyroidism is based on low concentrations of total and ionized calcium (< 1,5 mmol/L and < 0,8 mmol/L, respectively) and PTH. Serum calcium levels can be affected by laboratory errors, animal age, acid-base status, and plasma protein concentrations (Greco, 2012). Ionized calcium is the biologically active form of calcium, and by definition, clinical hypocalcemia is a consequence of ionized hypocalcemia. As the total calcium level does not directly correlate with ionized calcium and is not always a reliable indicator of clinical hypocalcemia, directly measuring ionized calcium is preferred whenever possible (Sharp *et al*., 2009). The balance between ionized calcium and protein-bound calcium is affected by pH. Acidosis increases the ionized fraction, while alkalosis decreases ionized calcium. In contrast, total calcium concentration is not affected by changes in pH. Therefore, an animal with acidosis may not show clinical signs of hypocalcemia, even though total serum calcium levels are low enough to expect a response from the patient. In contrast, an animal with alkalosis may show signs of hypocalcemia with total calcium levels within the reference range (Dhupa; Proulx, 1998).

In primary hypoparathyroidism, the PTH concentration is expected to decrease to a value below or within the reference range (20 a 65 pg/mℓ, in dogs), although the value is inappropriately low in relation to serum calcium content, concomitantly. The parathyroid panel presented in the present report revealed an inappropriately low PTH concentration <0.50 pmol/L (ref. 1,10 a 10,60 pmol/L) with a low total

calcium concentration of 4.0 mg/dl (ref. 8,0-12,0 mg/dl) and ionic concentration of 0.76 mmol/L (1,5 a 1,38 mmol/L), which was confirmatory for primary hypoparathyroidism. Ionized magnesium was included in the parathyroid panel because it is a cofactor for PTH secretion. Suppressed parathyroid secretion with concomitant hypocalcemia and hyperphosphatemia has been documented in cases of severe magnesium deficiency (Hitoshi *et al.*, 1997; Feldman; Nelson, 2004). However, this was considered unlikely in this case because the dog's iMg and phosphorus concentrations were within reference limits.

Treatment of hypoparathyroidism must be immediate, to reverse clinical manifestations, and long-term to prevent reappearance (Cardoso, 2015). In some cases, hypocalcemia confirmation is not immediate, as laboratory tests are required; however clinical signs must be controlled. Administration of diazepam (0,3 mg/kg/IV/BID) is recommended when there are persistent seizures despite adequate therapy.

In this case calcium gluconate doses (50 mg/Kg/IV) were administered to control acute neuromuscular signs with immediate improvement. Several studies have mentioned this can completely resolve behavioral signs, may take an additional 2 to 4 hours (Wolf *et al.*, 2020).

In most cases, maintenance therapy for primary hypoparathyroidism consists of permanent oral administration of vitamin D and calcium (Cardoso, 2015). In many cases, calcium supplementation is initiated and stopped because the dietary calcium is sufficient to meet an animal's needs. Oral vitamin D supplementation promotes both intestinal calcium absorption and renal calcium reabsorption, leading to a subsequent reduction in the need for oral supplementation. Calcitriol is the most commonly used drug administered for 3–5 days (Refsal *et al.*, 2001; Russell *et al.,* 2006).

During treatment in this case, large daily doses of vitamins were required, the clinical response of which was favorable and associated with the clinical results and serum levels of total and ionic calcium, which during hospitalization was, in some instances, below the reference range. The vitamin D dose effectively stabilized this patient. Hypercalcemia is the most common complication of vitamin D and calcium supplementation in dogs with hypoparathyroidism; however, this was not observed during treatment (Refsal *et al.*, 2001; Schaer *et al.*, 2001; Feldman; Nelson, 2004; Russell *et al.,* 2006).

CONCLUSIONS

The present report emphasizes the complexity of symptoms for primary hypoparathyroidism in dogs, highlighting careful diagnostic differentiation and treatment effectiveness with calcium gluconate, oral vitamin D, and calcium supplementation.

The prognosis of primary hypoparathyroidism primarily depends on an owner dedication and the veterinarian experience. Prognosis is excellent with appropriate therapy.

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