Diagnosing and treating parathyroid diseases in small animals: an update

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Ian Ramsey, Trish Ward discuss the disease, including primary and secondary hyper and hypo forms, looking at diagnosis as well as treatment of the condition

THE parathyroid gland plays a central role in regulating calcium ions by the production of parathyroid hormone (PTH).

PTH produces the active form of vitamin D (1,25-dihydroxycholecalciferol) and, together, they have the general action of increasing the biologically active, ionised form of serum calcium (and, therefore, increasing total serum calcium).

Parathyroid diseases may be split into primary and secondary hyper and hypo-parathyroidism. In addition, pseudohyperparathyroidism, caused by the production of PTH-related protein (PTHrP) by neoplastic cells, is associated with hypercalcaemia of malignancy – the most common cause of hypercalcaemia in cats and dogs[1],[2],[3].

Primary hyperparathyroidism

This is a rare disorder typically seen in animals more than seven years of age, with no gender predisposition. There is a significant breed predisposition for Keeshonds in the US[4], but in a UK study only four out of 29 dogs were Keeshonds[5]. The most common cause is a solitary functioning adenoma in one of the four parathyroid glands. Adenocarcinomas and generalised adenomatous hyperplasia have also been identified. Adenomatous chief cells autonomously secrete excessive

PTH, which increases osteoclastic activity, causing hypercalcaemia. Unaffected parathyroid glands are atrophic and non-functional.

The main clinical signs of the persistent hypercalcaemia are polyuria/polydipsia and lethargy/ weakness. The hypercalcaemia also causes decreased motility of smooth muscle of the gastrointestinal tract, resulting in vomiting or constipation. Urolithiasis (including bladder and renal calculi) is described with a high frequency in one series of dogs[4], but less so in the UK[5].

Seizures and muscle tremors may be seen occasionally. A palpable cervical nodule may be present. In adult dogs, it will take a long time before clinical signs of excess PTH activity develop in bone, such as pain and pathological fractures, and such signs are rare. In many cases, clinical signs are mild and may not be identified until after hypercalcaemia is inadvertently discovered during a preanaesthetic profile. Some cases are completely asymptomatic.

Diagnosis

The most common clinicopathological abnormality is persistently increased total and ionised calcium concentrations. Hypophosphataemia is seen in only 20 to 30 per cent of affected dogs, despite the anticipated effect of PTH on renal tubular phosphorous excretion. More common secondary causes of hypercalcaemia must be completely eliminated before a diagnosis of primary hyperparathyroidism is made (see below). Some laboratories offer PTH and PTHrP measurements. Blood samples must be taken into EDTA tubes, then immediately centrifuged and the supernatant separated and frozen (in a serum tube). Contact the laboratory to arrange for suitable transport containers to be sent for sample submission.

High-resolution ultrasonography has identified hyperplastic parathyroid glands and parathyroid adenomas in dogs. Surgical exploration of the cervical region may be indicated in some cases.

Treatment of hypercalcaemia

Therapy directed towards the underlying cause is the only consistent means of long-term management of the hypercalcaemia associated with hyperparathyroidism. Supportive therapy is often required to temporarily decrease serum calcium concentrations until a definite diagnosis is made. Many animals with hyperparathyroidism have been hypercalcaemic for weeks before the abnormality is discovered and emergency treatment is not needed.

The clinical status determines the intensity of the treatment regimen. Animals exhibiting dehydration, azotaemia, hyperphosphataemia, neurological signs, cardiac arrhythmias or serum calcium concentration greater than 4µmol/L generally require immediate therapy. IV fluid therapy with normal saline (0.9 per cent), at two to three times the maintenance rate, is recommended. Once rehydrated, continued saline diuresis will enhance calcium excretion. Careful monitoring for signs of fluid overload and hypokalaemia is essential. If hypercalcaemia persists, frusemide is

recommended.

Treatment of parathyroid tumours

Surgical removal of the parathyroid mass should be performed, if possible. The dog or cat must be carefully monitored for signs of hypocalcaemia after surgery. Alternative treatments include ultrasound-guided ethanol or heat ablation, but success rates are lower and complications are not unknown[6].

When surgery is not an option, glucocorticoids may be effective due to their nonspecific effects on calcium homeostasis. They inhibit calcium resorption from bone, promote renal excretion of calcium, and counteract the effects of vitamin D, resulting in mild decreases in calcium concentration. However, glucocorticoid therapy should be avoided until a specific diagnosis has been made, as it can obscure detection of lymphoma and reduce subsequent response to chemotherapy. The use of other treatments, such as bisphosphonates, has not been reported in primary hyperparathyroidism.

Secondary hyperparathyroidism (renal, nutritional, thyroid and adrenal)

Secondary hyperparathyroidism is a response to a lowering of serum calcium levels or as a result of a direct stimulus (such as an increase in serum phosphate or cortisol) of PTH production – such that PTH is increased, but calcium usually remains within the reference range. It occurs in chronic renal failure because of the retention of serum phosphate, where there is a lack of calcium in the diet of young animals resulting in juvenile osteoporosis, in cats with hyperthyroidism and in dogs with hyperadrenocorticism (resulting in calcinosis cutis and calcium containing uroliths)[2],[7],[8],[9],[10],[11],[12].

Primary hypoparathyroidism

Spontaneous hypoparathyroidism is a rare disorder, usually resulting from lymphocytic parathyroiditis. It occurs at any age, with a possible female predisposition in dogs. Clinical signs are usually of acute-onset intermittent neurological or neuromuscular disturbances resulting from hypocalcaemia[10],[13]. Cataract formation is common.

In practice, the most common form of primary hypoparathyroidism is seen after bilateral thyroidectomy in hyperthyroid cats if the parathyroid glands are injured, devascularised or inadvertently removed. Hypocalcaemia is a significant cause of mortality in such cases if not recognised. The cats usually become anorexic, vocalise, twitch and, if untreated, exhibit seizures/convulsions.

Treatment of hypocalcaemia

Low blood calcium is a common response to thyroid surgery, and treatment should not be instituted unless clinical signs are observed. In clinically affected animals, calcium should initially be administered slowly intravenously, while simultaneously auscultating the heart. If bradycardia develops, the injection should be stopped.

Once clinical signs have stabilised, then a continuous infusion of calcium in isotonic saline is started. Oral therapy is started as soon as it can be tolerated. Active vitamin D analogues, such as dihydrotachysterol (AT 10) or calcitriol (Rocaltrol), are required for the long-term therapy because calcium uptake from the gastrointestinal tract is dependent on vitamin D (but activation of vitamin D requires PTH). In traumatic hypoparathyroidism, which is rarely permanent, the dihydrotachysterol can be decreased slowly while monitoring calcium once the calcium concentration has been stable for a month.

Secondary hypoparathyroidism

Diseases associated with hypomagnesaemia (for example, protein-losing enteropathies) will result in hypocalcaemia due to a decrease in PTH. Treatment of the hypomagnesaemia results in normalisation of PTH and calcium concentrations[14].

Pseudohyperparathyroidism

Malignancy-associated hypercalcaemia is a well-studied paraneoplastic syndrome. Isolated hypercalcaemia should always prompt thorough investigation for occult neoplasia, even when the initial database shows no evidence of neoplasia.

Paraneoplastic hypercalcaemia occurs in 10 to 40 per cent of dogs with lymphoma (most commonly the mediastinal form) and in 80 to 90 per cent of dogs with perianal apocrine gland adenocarcinomas. A direct correlation between T-cell phenotype lymphomas and hypercalcaemia has also been reported. Hypercalcaemia of malignancy is caused by the release of PTHrP with a compensatory, secondary hypoparathyroidism[15],[16]. PTHrP has a similar structure to PTH, but is the result of expression of a different gene.

It is now viewed as a normal protein that is over-expressed in certain tumours. It is an important regulator of placental calcium transport in the foetus, and it appears to be a physiological modulator of smooth muscle tone. However, in adults it is normally undetectable in serum by current assays. Hypercalcaemia of malignancy occurs in both cats and dogs, but is more common in dogs[17]. The severity of the hypercalcaemia is notably worse in these cases than with other causes of hypercalcaemia. Malignancy-associated hypercalcaemia generally conveys a poor prognosis.

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