Primary Hyperparathyroidism

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Profile

- Primary hyperparathyroidism (PHPT) and primary hypoparathyroidism are the most common primary parathyroid gland diseases.
- Two external parathyroid glands lie outside the thyroid capsule, and two internal parathyroid glands are embedded within the thyroid parenchyma.¹
- Parathyroid glands synthesize and secrete parathyroid hormone (PTH) from chief cells.²
  - PTH increases plasma calcium concentration by mobilizing calcium from bone, increasing renal calcium reabsorption, and promoting formation of calcitriol, which increases intestinal calcium absorption.
  - PTH promotes phosphaturia by decreasing renal phosphorus reabsorption.
- Parathyroid gland diseases are characterized by abnormalities in serum calcium and phosphorus concentrations.
- Clinical signs are frequently secondary to serum calcium abnormalities.
- Parathyroid glands may also be affected secondary to other disease states (eg, renal secondary hyperparathyroidism).

Definition & Pathophysiology³,⁴

- Excessive PTH production from autonomously functioning chief cells, usually in a single parathyroid adenoma
- Parathyroid carcinoma, hyperplasia, or multiple parathyroid adenomas are possible but rare.

Systems

- Urinary, neuromuscular, and GI signs are possible.

Incidence & Prevalence

- Accounts for ~13% of dogs with ionized hypercalcemia⁵
- PHPT is caused by adenoma of the parathyroid gland (75%–85% of cases), hyperplasia (5%–15% of cases), and carcinoma (5%–10% of cases).⁴,⁶,⁷
- Rarer in cats⁶
  - More common causes of hypercalcemia in cats include renal failure and idiopathic hypercalcemia (Table, next page).

Signalment

Breed Predilection

- Autosomal dominant inheritance causes increased prevalence in keeshonds,⁹ but PHPT should be considered as a differential for any dog or cat with hypercalcemia.

Age & Range

- Middle-aged to geriatric dogs

Sex Predilection

- No known predilection

Clinical Signs³,⁶

- Mainly attributable to hypercalcemia, which may be found incidentally:
  - Up to 35% of patients show no clinical signs.

Parathyroid gland diseases are characterized by abnormalities in serum calcium and phosphorus concentrations.

See the companion article Primary Hypoparathyroidism on page 15 of this issue.

For More
Affected patients often appear healthier than those with other causes of hypercalcemia (eg, lymphoma).

Causes(s) and approximate frequency of clinical signs:
- Polyuria/polydipsia from decreased renal tubular response to antidiuretic hormone (50%–60%)
- Hematuria, stranguria, pollakiuria, urinary tract infection, and urinary tract obstruction (50%)
- Calcium phosphate or oxalate urolithiasis may result from calciuria and phosphaturia.

Dilute urine-specific gravity predisposes patients to infection.
- Lethargy, muscle wasting, and stiffness from decreased neuromuscular tissue excitability (40%–45%)
- Inappetence (37%), vomiting (13%), and constipation (6%) caused by decreased excitability and motility of GI smooth muscle.

A palpated mass could represent an alternative cause of hypercalcemia (eg, thyroid carcinoma).

Examination should not identify any finding consistent with other causes of hypercalcemia (eg, lymphadenopathy).

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**Physical Examination**
- Patients may appear lethargic or weak.
- A cervical mass may be palpated in cats.
- A palpable parathyroid mass is rare in dogs.

**Diagnosis**

**Definitive**
- Histologic examination of parathyroid gland mass(es) following successful surgical removal/ablation and resolution of hypercalcemia

**Table: Differential Diagnoses for Hypercalcemia & Hypocalcemia**

<table>
<thead>
<tr>
<th>Differential</th>
<th>Hypercalcemia</th>
<th>Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anomalous</strong></td>
<td>Idiopathic hypercalcemia of cats*</td>
<td>Eclampsia,* intestinal malabsorption,* vitamin D deficiency, magnesium deficiency, acute kidney injury,* chronic kidney disease,* nutritional secondary hyperparathyroidism (eg, feeding a high-phosphorus, low-calcium diet), primary hypoparathyroidism secondary to another cervical disease</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Acute kidney injury,* chronic kidney disease,* hypoadrenocorticism,* primary hyperparathyroidism secondary to adenomatous gland hyperplasia</td>
<td>Medullary thyroid carcinoma, tumor lysis syndrome, osteoblastic bone tumors</td>
</tr>
<tr>
<td><strong>Neoplastic</strong></td>
<td>Lymphoma,* anal sac adenocarcinoma,* primary hyperparathyroidism related to parathyroid adenoma* or carcinoma, multiple myeloma, leukemia, other carcinomas, thymoma, metastatic or primary bone tumors (eg, osteosarcoma)</td>
<td>Vitamin D toxicity</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>Granulomatous disease, canine angiostrongylosis (caused by Angiostrongylus vasorum infection), osteomyelitis</td>
<td>Sepsis,* trauma, pancreatitis,* primary hypoparathyroidism resulting from immune-mediated destruction or iatrogenic following PHPT surgery or sudden correction of hypercalcemia</td>
</tr>
<tr>
<td><strong>Immune mediated</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Iatrogenic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toxic</strong></td>
<td>Vitamin D toxicity</td>
<td>Ethylene glycol toxicity</td>
</tr>
<tr>
<td><strong>Nonpathologic</strong></td>
<td>Immaturity,10 lipemia, laboratory error, excessive calcium supplementation, thiazide treatment</td>
<td>Hypoalbuminemia,* laboratory error, phosphate-enema administration, transfusion with citrate-anticoagulated blood, EDTA sample contamination, sodium bicarbonate administration</td>
</tr>
</tbody>
</table>

*Denotes common cause
Plasma PTH can be measured to support diagnosis.

Differentials
- Differential diagnoses for hypercalcemia can vary (Table).

Laboratory Findings
- Chemistry panel: total hypercalcemia, decreased or borderline-low serum phosphorus concentration, possible azotemia
- Ionized hypercalcemia in >90% of cases
- Urinalysis: frequent hyposthenuria or isosthenuria
- Crystalluria, bacteriuria, hematuria, and pyuria are possible.

Imaging
- Ventral neck ultrasonography may identify parathyroid masses (Figure 1).
- Most masses are small (4–9 mm in diameter).
- Ultrasonography can be highly sensitive and is operator-dependent.
- Parathyroid scintigraphy with Technetium (99mTc) sestamibi, nuclear medicine imaging, can identify hyperfunctional parathyroid tissue in patients with negative ultrasound findings but may show poor sensitivity and specificity in dogs.11
- Abdominal ultrasonography may reveal urinary tract calculi or other lesions causing hypercalcemia (eg, lymphoma).
- Plain radiography may reveal radiopaque urinary calculi or intrathoracic lesions causing hypercalcemia (eg, anterior mediastinal mass).

Other Diagnostics
- Plasma PTH concentration
  - Values that are increased or in the upper half of reference range are consistent with PHPT in hypercalcemic patients, which should have low PTH values.
- Serum PTH-related peptide concentration
  - Identifies most cases of hypercalcemia of malignancy

Medical
- No definitive medical cure
- Medical therapy can ameliorate severe hypercalcemia signs before definitive treatment or can be used to treat or prevent postoperative hypocalcemia following parathyroid nodule removal or ablation (see Hypercalcemia: Treatment Basics and Prevention & Treatment of Hypocalcemia, next page).

Surgical & Interventional
- Three definitive treatments are described:
  - Surgical parathyroidectomy
    - Mass(es) should be located preoperatively using imaging.
    - Success rate, 89%–96%6,12
  - Percutaneous ultrasound-guided radiofrequency heat ablation
    - Nodule is destroyed by thermal necrosis from radiofrequency waves applied through IV catheter under ultrasound guidance.
    - Equipment is expensive.
    - Success rate, 81%–92%12,13
  - Percutaneous ultrasound-guided ethanol ablation
    - Ethanol is injected into the nodule with ultrasound guidance, causing coagulation necrosis.
    - Used less frequently because of lower success rates (~72%)12
- Parathyroidectomy is most commonly used by the authors, but preferred treatment method depends on local expertise and experience.

Treatment
- Definitive treatment requires removal or ablation of parathyroid mass(es).

Follow-up

Patient Monitoring
- Patients should be hospitalized with limited exercise for ≥5 days postoperatively to minimize risk and monitor for hypocalcemia.
- Total and ionized serum calcium concentrations should be measured q12–24h for ≥5 days postoperatively.
Slightly low serum calcium concentration (8–10 mg/dL) should be maintained to prevent iatrogenic hypocalcemia and promote return of parathyroid function.4

If given, vitamin D and calcium therapy should be tapered and discontinued over 3–5 months, starting 14 days after treatment is initiated.
- Serum calcium should be measured before each reduction.

Complications4,7
- Postoperative hypocalcemia can occur 4–7 days posttreatment in up to 30% of patients.
- May develop after any treatment method
- Causes signs in up to 10% of patients
- Hypocalcemia risk may correlate with duration and magnitude of preoperative hypercalcemia, but currently there is no method for identifying which patients will be affected.14
- Horner syndrome and transient laryngeal paralysis have been reported following ultrasound-guided treatment.

In General

Relative Cost
- Definitive treatment can be expensive, especially if patient requires cystotomy or has clinical hypocalcemia after treatment: $$$$$
- Surgical parathyroidectomy: $$$$$
- Percutaneous ultrasound-guided radiofrequency heat ablation: $$$$
- Percutaneous ultrasound-guided ethanol ablation: $$$$

Cost Key
$ = up to $100
$$ = $101–$250
$$$ = $251–$500
$$$$ = $501–$1000
$$$$$ = more than $1000

Prognosis
- Excellent with appropriate management
- Definitive treatment is curative in most cases.
- Approximately 10% of patients have recurrence.46

Prevention & Treatment of Hypocalcemia4

Prevention
- PO calcium and vitamin D supplementation initiated 1–2 days preoperatively can decrease risk for postoperative hypocalcemia and may be appropriate in patients with marked preoperative hypercalcemia.
- Commonly used forms of vitamin D are calcitriol (0.03–0.06 µg/kg/day) or dihydrotachysterol (0.02–0.03 mg/kg/day).
  • Calcitriol tablets require compounding for smaller patients.
  • Dihydrotachysterol, not available in the U.S., has a longer half-life than calcitriol; both can cause hypercalcemia if oversupplementation occurs.

Treating Postoperative Clinical Hypocalcemia
- 10% calcium gluconate (5–15 mg/kg) IV can be administered over 10–30 minutes with ECG monitoring.
- This can be followed with continuous IV infusion of 10% calcium gluconate (60–90 mg/kg/day) to prevent signs while PO vitamin D is initiated.
- Intermittent boluses may be safer because of risk for tissue necrosis following extravasation.

Treating Postoperative Hypocalcemia in Patients Without Clinical Signs
- PO vitamin D and calcium therapy is suggested if serum total calcium concentration is <8.5 mg/dL or serum ionized calcium concentration is <0.8 mmol/L.

See Aids & Resources, back page, for references & suggested reading.