Investigating disorders of hypercalcaemia

BERNARD CHAMPION BEc, MB BS, BSc(Med)(Hons 1), FRACP, MMedEd
ALICE TANG MB BS, BSc(Med)

This endocrine education section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems.

Disorders of hypercalcaemia are relatively common. Primary hyperparathyroidism (PHPT) has an incidence of 1 to 20 per 1000,[1] and up to 20% of patients with cancer will experience hypercalcaemia.[2] Under normal physiological conditions, calcium metabolism revolves around three key organs – bone, gut and kidneys – to maintain total serum calcium levels between approximately 2.2 and 2.5 mmol/L. This occurs via a series of feedback loops from the key hormones parathyroid hormone (PTH) and 1,25-hydroxyvitamin D, with additional influences from other agents including calcitonin, phosphate, magnesium and calcium itself. A number of inherited or acquired disorders can upset this homeostasis, leading to manifestations of biochemical or clinical hypercalcaemia. Although the list of potential causes of hypercalcaemia is quite long (see the box on this page), most cases are due to either PHPT or a malignancy of haematological or epithelial type. It is useful to determine whether hypercalcaemia is PTH-dependent or not. The following series of three case vignettes will differentiate and explain these disorders.

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Dr Champion is an Endocrinologist and Dr Tang is an Endocrinology Advanced Trainee at the Department of Endocrinology, Nepean Hospital and The University of Sydney, Sydney, NSW.

Case 1

A 45-year-old woman presents with lethargy, nocturia, nonspecific aches and constipation of several month' duration. She takes no medication, and has no past history or family history of hypercalcaemia, nephrolithiasis or osteoporosis. Full blood count, electrolyte levels, liver function tests and inflammatory markers are normal. Other results show:

- ***corrected calcium level: 2.92 mmol/L (normal range: 2.15–2.55 mmol/L)***
- ***phosphate level: 1.0 mmol/L (normal range: 0.85–1.4 mmol/L)***
- ***magnesium level: 0.7 mmol/L (normal range: 0.8–1.1 mmol/L)***
- ***serum creatinine level: 70 µmol/L (normal range: <110 µmol/L).***

This patient has symptomatic hypercalcaemia, with typically low-normal phosphate level, low magnesium level and normal renal function. Symptoms generally correlate to the degree of chronic hypercalcaemia and in addition to those listed above may include polydipsia and polyuria, depression, confusion, dehydration and renal failure. Associations include nephrolithiasis, nephrocalcinosis, osteoporosis, pancreatitis, diabetes, obesity, gout, hyperlipidaemia and gastrointestinal ulceration.[3]

What are the initial investigations that should be ordered?

This woman needs her serum PTH level checked to determine whether this is PTH-dependent or PTH-independent hypercalcaemia. Baseline 25-hydroxyvitamin D level should also be checked. The results show:

- 25-hydroxyvitamin D level: 61 nmol/L (normal range: 50–140 nmol/L)
- PTH level: 16.2 pmol/L (normal range: 2–7 pmol/L).

Causes of hypercalcaemia

PTH-dependent (PTH levels will be high-normal or elevated)

- Primary hyperparathyroidism
  - parathyroid adenoma
  - parathyroid carcinoma
- Parathyroid hyperplasia
  - chronic renal failure
  - lithium
- Genetic disorders
  - familial hypocalciuric hypercalcaemia (FHH)
  - multiple endocrine neoplasia type 1
  - CDC73-related disorders (familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumour syndrome)

PTH-independent (PTH levels will be low-normal or suppressed)

- Malignancy
  - humoral hypercalcaemia of malignancy (PTHrP, other cytokines)
  - haematological malignancies (e.g. multiple myeloma)
  - osteolytic hypercalcaemia (bone metastases)
- Drug induced
  - increased renal resorption (e.g. thiazides)
  - increased gut absorption (e.g. calcitriol, milk-alkali syndrome)
  - increased bone turnover (e.g. oestrogens, antioestrogens, androgens and progestins)
- High bone turnover states
  - hyperthyroidism
  - phaeochromocytoma
  - immobilisation
  - Addison's disease
- Ectopic 1-α hydroxylase production (elevated 1,25-dihydroxyvitamin D levels)
  - granulomatous disease (e.g. sarcoidosis, tuberculosis)
  - lymphoma

ABBREVIATIONS: PTH = parathyroid hormone; PTHrP = parathyroid hormone-related protein.

The elevated PTH level indicates PTH-dependent disease. The rare genetic condition of familial hypocalciuric hypercalcaemia (FHH) is unlikely in this woman because of her symptoms, the absence of a family history of hypercalcaemia, the relatively high serum calcium level and the PTH level more than twice the upper level of normal. As such, urine calcium analysis is not required.

What further investigations should be ordered?

If surgery is being considered, localisation studies looking for a parathyroid adenoma with ultrasound and technetium 99m sestamibi scan should be undertaken. These have a combined sensitivity of about 80 to 95% and specificity of about 90% in experienced centres; these may be lower in nondedicated centres.[4] MRI or high-resolution CT may be considered in difficult cases. Preoperative adenoma localisation can facilitate minimally invasive parathyroidectomy over bilateral neck exploration leading to reduced surgical costs.[4]

What is the diagnosis?

The clinical picture and biochemistry are enough to diagnose PHPT regardless of the outcome of localisation studies.

What does the patient's technetium 99m sestamibi scan show (see Figure above)?

Technetium 99m sestamibi scan (see arrow) and ultrasound both indicate a likely small right inferior parathyroid adenoma.

How should this patient be managed?

Surgery is indicated for symptomatic PHPT due to an adenoma whether it is localised on imaging studies or not. Indications for surgery in asymptomatic PHPT include age less than 50 years, corrected calcium level 0.25 mmol/L or more above the upper limit of normal, osteoporosis or worsening renal impairment (estimated glomerular filtration rate <60 mL/min).[5] Parathyroidectomy via bilateral neck exploration by an experienced surgeon cures 95 to 99% of patients, with a complication rate of less than 3%.[4]

When surgery is refused or contraindicated, medical therapy with calcimimetic cinacalcet may be considered. At a dose of 30 mg titrated to a maximum of 180 mg once daily, cinacalcet can decrease PTH level by about 30% and serum corrected calcium level by about 10%.[3] It has little effect on bone density. In Australia it has PBS listing only for renal hyperparathyroidism and hence must be hospital or self-funded for use in patients with PHPT. Oral or intravenous bisphosphonates have been shown to increase bone density but have little effect on serum calcium level. They are not routinely recommended for use in patients with PHPT,[3] except if they are being used to treat co-incident osteoporosis in those with mild PHPT or if a patient is unable or unwilling to have surgery.

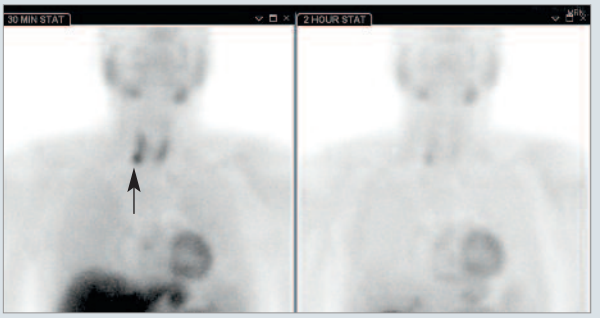

Figure. Technetium 99m sestamibi scan in Case 1, showing a right inferior pole parathyroid adenoma (arrow).

Case 2

A 65-year-old woman presents with lethargy, nocturia, nonspecific aches, constipation and weight loss evolving over several weeks. She is not taking any medications and has no past history or family history of hypercalcaemia, nephrolithiasis or osteoporosis. Full blood count, electrolyte levels and liver function tests are normal. Other results show:

- ***corrected calcium level: 3.2 mmol/L (normal range: 2.15–2.55 mmol/L)***
- ***phosphate level: 0.7 mmol/L (normal range: 0.85–1.4 mmol/L)***
- ***magnesium level: 0.7 mmol/L (normal range: 0.8–1.1 mmol/L)***
- ***serum creatinine level: 115 µmol/L (normal range: <110 µmol/L)***
- ***erythrocyte sedimentation rate (ESR): 85 mm/h (normal range: <20 mm/h).***

This patient has symptomatic hypercalcaemia, low phosphate and magnesium levels and mild renal impairment.

What investigations should be ordered?

This woman needs her serum PTH level checked to determine whether this is PTH-dependent or PTH-independent hypercalcaemia. A baseline serum 25-hydroxyvitamin D should also be checked. Her elevated ESR raises concern of an underlying inflammatory, infectious or malignant process. The results show:

- 25-hydroxyvitamin D level: 75 nmol/L (normal range: 50–140 nmol/L)
- PTH level: <1 pmol/L (normal range: 2–7 pmol/L).

The suppressed PTH levels indicates PTH-independent disease. This woman requires further investigation to exclude malignancy.

What are the differential diagnoses?

Differential diagnoses for this case include multiple myeloma, breast cancer, gynaecological cancers, lung cancer and lymphoma; malignant hypercalcaemia has been reported with many different cancers.[2]

What further investigations are required?

Parathyroid imaging is not required in this case. Some laboratories offer testing for PTH-related protein (PTHrP), which is the most common substance causing humoral hypercalcaemia of malignancy; however, this is not clinically required in most cases. The initial step usually involves ordering serum and urine immune-electrophoretogram to look for evidence of a monoclonal gammopathy; if this is negative, bone scintigraphy looking for solid tumour bone metastases should be performed.

Serum electrophoresis identifies a 20 g/L monoclonal paraprotein (IgG kappa) with Bence Jones protein present in the urine. Further workup for likely myeloma is indicated, including skeletal survey and haematology referral for bone marrow biopsy and staging.

What is the diagnosis?

Malignant hypercalcaemia secondary to multiple myeloma.

How should this patient be managed?

Patients with symptomatic malignant hypercalcaemia should be treated with normal saline diuresis, which also aids calciuresis. Frusemide diuresis is often added, but clinical evidence of efficacy is lacking.[1] If hypercalcaemia persists despite saline diuresis, an intravenous bisphosphonate (usually zoledronic acid) may be used provided there are no absolute contraindications, such as end stage renal disease or severe active dental disease.

Case 3

A 35-year-old woman presents with lethargy but is otherwise well. She is not taking any medications. She has no past history or family history of nephrolithiasis or osteoporosis, but she reports that her father had surgery many years ago for a 'calcium problem'. Full blood count, electrolyte levels, iver function tests and inflammatory markers are all normal. Her other test results show:

- ***corrected calcium level: 2.72 mmol/L (normal range: 2.15–2.55 mmol/L)***
- ***phosphate level: 1.0 mmol/L (normal range: 0.85–1.4 mmol/L)***
- ***magnesium level: 1.0 mmol/L (normal range: 0.8–1.1 mmol/L)***
- ***serum creatinine level: 60 µmol/L (normal range: <110 µmol/L).***

What do these results suggest?

This woman has asymptomatic mild hypercalcaemia with a low-normal phosphate level, but a normal magnesium level in the presence of normal renal function. PHPT due to a sporadic adenoma should be considered; however, the family history suggests a potential genetic cause, and the patient is quite young.

What further investigations should be ordered?

This woman needs her serum PTH level checked to determine whether this is PTH-dependent or PTH-independent hypercalcaemia. A baseline serum 25-hydroxyvitamin D level and 24-hour urinary calcium excretion should also be checked. The results of these tests show the following:

- 25-hydroxyvitamin D level: 68 nmol/L (normal range: 50–140 nmol/L)
- PTH level: 6.6 pmol/L (normal range: 2–7 pmol/L)
- 24-hour urinary calcium: fractional excretion of calcium 0.7%.

What do these results suggest?

The high-normal PTH indicates PTH-dependent disease as the PTH level is inappropriately high for her serum calcium level. The clinical scenario and low urinary calcium excretion are consistent with FHH. Magnesium levels are often preserved in patients with FHH as opposed to the low levels seen in those with PHPT. Calcium to creatinine clearance ratio is usually more than 0.02 in patients with PHPT and less than 0.01 in those with FHH, although some crossover can occur. A spot fasting urine calcium excretion can be used, which is usually less than 30 µmol/L in FHH.[6] Even with this measure, crossover between FHH and PHPT can occur. Hence interpretation of urinary calcium results needs to occur in conjunction with careful consideration of the serum PTH level and the overall clinical picture.[7]

What should happen next?

FHH is caused by an inactivating mutation in the calcium sensing receptor, leading to reactive parathyroid gland hyperplasia with mild elevation of PTH levels (rarely more than two times the upper limit of normal).[6] It is generally benign and rarely causes symptoms, complications of hypercalcaemia or adenoma formation. Localisation studies and surgical referral are not indicated as the defect is in all tissues containing the calcium sensing receptor rather than a single parathyroid gland. Unfortunately, such patients are not always identified, and may undergo surgical referral. Referral of the patient to a clinical genetics service for counselling and consideration of FHH gene testing is indicated.

What is the diagnosis?

Mild asymptomatic hypercalcaemia due to presumed FHH.

What is the outcome?

Gene testing returned positive for a mutation in the calcium sensing receptor. Counselling and screening of other first-degree relatives was undertaken.

Although FHH is a rare condition it is important to identify such patients and their family cohorts to avoid inappropriate investigation and management. Such patients will usually remain asymptomatic and do not experience hypercalcaemic complications.[8] They should undergo genetic counselling and family screening with annual observation of calcium and PTH levels.

Summary

Hypercalcaemia is a relatively common disorder. Any patient with a high corrected serum calcium level should have further testing, including repeat measurement of calcium, magnesium, phosphate and 25-hydroxyvitamin D levels, renal function tests and simultaneous measurement of PTH levels, to see if there is PTH-dependent or PTH-independent disease. This will determine the appropriate path of investigation, referral and management. **ET**

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COMPETING INTERESTS: None