Investigation and Management of Primary Hyperparathyroidism

Hypercalcemia is a common laboratory finding. In most cases the differential diagnosis can be separated into parathyroid dependent disease, which is most commonly due to Primary Hyperparathyroidism or parathyroid independent disease, which is most often due to malignancy.

In 2008 in Australia, Primary Hyperparathyroidism (PHPT) is commonly, asymptomatic, long-standing and if symptoms arise, the most common presentation is with either renal stone formation or minimal trauma fractures. Consensus guidelines regarding the diagnosis of PHPT were last published in 2002 and it is worth summarising these recommendations as well as providing some local Australian recommendations (1).

Free ionised calcium

Total calcium, corrected for serum albumin, is routinely used as an estimate of the free or ionised calcium concentration. In several case series, the direct measurement of ionised calcium has been found to be more sensitive than total corrected calcium in the diagnosis of PHPT (2). One other important reason to measure ionised calcium is to confirm an elevated corrected total calcium result. Consequently, at Clinipath Pathology, in patients suspected of suffering from hypercalcemia or who have an elevated corrected total calcium, assessment of ionised calcium is recommended. The main limitation of ionised calcium measurement is the need to measure ionised calcium using a fresh dedicated sample ideally collected after an overnight fast.

Parathyroid hormone (PTH)

Once hypercalcemia has been confirmed, measurement of PTH is advised. An elevated intact PTH result which is 1-2 times elevated is typical of PTH dependent disease. Even an intact PTH result within the upper half of the reference limits is regarded as inappropriate in the setting of hypercalcemia and supportive of the diagnosis of PTH dependent hypercalcemia (3).

In PTH independent disease, intact PTH results will often be suppressed. PTH related peptide (PTHrP) which is secreted by many tumours, does not cross react in intact PTH assays. At Clinipath Pathology, PTH is ideally measured in a fresh serum sample because the hormone is unstable in stored samples.

Consider the differential diagnosis

The differential diagnosis of PTH dependent hypercalcemia includes primary hyperparathyroidism (PHPT), due to a solitary adenoma or diffuse hyperplasia, lithium therapy, Familial Hypocalciuric Hypercalcemia (FHH) or tertiary hyperparathyroidism associated with renal failure.

Parathyroid cancer is a common concern of patients but this condition is extremely rare (<0.5%). In the absence of a palpable neck mass or markedly elevated intact PTH results (typically > 4-5 times elevated above the upper reference limit in a patient with normal renal function), parathyroid cancer can be excluded and the patient reassured. A review of medication use, assessment of renal function and enquiry regarding a family history of hypercalcemia is advisable to exclude other causes of PTH dependent hypercalcemia.

FHH and urine calcium assessment

Assessment of fasting urine calcium excretion (CaE) or 24 hour urine calcium/creatinine clearance ratio is needed (4). In FHH, CaE is typically less than 30 umol/L GFR (Glomerular filtration rate) and the 24 hour clearance ratio is characteristically less than 0.01. Furthermore, it is rare to see intact PTH results more than 2 fold elevated in FHH. The importance of recognising FHH is to avoid unnecessary surgical neck exploration as this disorder cannot be corrected surgically and is not associated with the same morbidity that is characteristic of PHPT. Occasionally, cases of PHPT can present with very low urine calcium results and a specialist opinion may be advisable (see later).

If screening tests suggest a diagnosis of FHH, it is advisable to measure ionised calcium, intact PTH and fasting urine CaE or 24 hour urine calcium creatinine clearance ratio in first degree family members (parents or siblings) as there is a 1 in 2 chance of siblings harbouring the same mutation and hence being hypercalcemic and having a low urine calcium excretion.

Since FHH may occur with a variety of CaSR mutations, a single genetic test is not available and therefore genetic testing is not helpful in the initial diagnostic algorithm.

Lithium therapy

In patients taking lithium and where it is safe to cease medication, withdrawal and retesting in 3 months is currently advised. Not all cases of lithium induced

Summary

- Ionised calcium should be measured to confirm hypercalcemia
- PTH is elevated or in the upper half of the reference limits in PHPT
- Urine calcium should be measured to exclude FHH
- Assess 25OHD and bone density in all cases with PHPT
- Consider surgical options or monitor 6 monthly
In PHPT, further investigation with bone mineral density (BMD) is advisable to assess future fracture risk. Fracture rates are increased at all sites and a BMD T score < -2.5 is one of the current criteria for surgical neck exploration.

Assessment of 25 hydroxyvitamin D is also advisable as vitamin D deficiency often coexists with primary hyperparathyroidism. In patients with 25OHD < 50 nmol/L, supplementation with cholecalciferol is suggested, although more frequent monitoring of serum calcium is advisable. In such cases, assessment of ionised calcium at 2 weeks, 1 month and then 3 monthly after starting cholecalciferol is one approach. Several short term studies have indicated that this approach appears safe and may result in a fall in intact PTH. For similar reasons, restriction of dietary calcium is unnecessary and may in fact result in worsening parathyroid disease.

Surgery for PHPT

Based on consensus recommendations, surgical treatment for PHPT could be offered if the patient is:

- young (<50 years of age),
- serum corrected total calcium is high (> 3 mmol/L or ionised calcium > 1.5 mmol/L),
- 24 hour urine calcium excretion is increased (>7.5 mmol/day),
- creatinine clearance is reduced (by > 30%),
- bone density is low (T score below -2.5 at hip, spine or forearm), or
- medical surveillance is not desirable or possible.

Where surgery is advisable and this is the initial presentation, preoperative localisation imaging studies are not required. Assessment of thyroid function and thyroid ultrasound imaging is advisable if focal enlargement of the thyroid is detected clinically and pragmatic if surgical neck exploration will proceed. The risks of laryngeal nerve injury and post surgical hypoparathyroidism should be explained and it is advisable to refer the patient to an experienced endocrine surgeon to minimise such risks. Postoperative hypocalcemia may occur due to hypoparathyroidism or hungry bone syndrome which is due to rapid skeletal uptake of calcium. Both conditions are best managed by an expert in the management of bone and calcium disorders and often require in patient management if symptomatic.

Surveillance in non-surgically managed patients

In patients that decline surgical neck exploration or do not meet the above criteria, routine surveillance with 6 monthly assessment of serum ionised calcium, PTH, creatinine/eGFR and annual BMD plus 25 OHD can be offered (see Table 1 over page).

Reasons to refer for a specialist opinion

- Doubt regarding diagnosis, especially where FHH is a possibility.
- Family history of hypercalcemia: other causes such as multiple endocrine neoplasia, jaw tumour syndrome etc should be considered in such cases.
- Doubt regarding surgical management options.
- Advice on medical management in patients suffering from symptomatic disease (renal stones, low BMD) and surgery is not advisable/possible.
- Postoperative hypocalcemia after surgical neck exploration (urgent/immediate referral advised).
- Recurrent PHPT which will require preoperative localisation studies (see Image A & B over page).
Medical management of PHPT

Medical management options include encouraging sufficient dietary calcium intake to attain current Australian recommendations (1000mg in adults and 1300mg in postmenopausal women and men over age 70), supplementation with cholecalciferol if 25 OHD is less than 50 nmol/L and consideration of bisphosphonates or raloxifene (in postmenopausal women) if fracture risk is increased.

Overview

The typical patient suffering from PHPT in Australia is asymptomatic. Approximately one in five patients with PHPT suffer classical symptoms with kidney stones or overt bone disease. Some patients report other symptoms which are non-specific, may not relate to the presence of PHPT and do not figure in decisions regarding surgical treatment. The link between cardiovascular disease (hypertension), gastrointestinal disease (peptic ulcers) or metabolic disease (diabetes mellitus) and PHPT is not clear or proven to be causal. The differential diagnosis of parathyroid dependent hypercalcemia should be considered, a review of surgical indications should be performed and in those patients not subjected to surgery, biannual surveillance should be instituted.

Table 1. Pathology and Radiology Investigations

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<thead>
<tr>
<th>Investigation</th>
<th>Pathology Abbreviation</th>
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<tr>
<td>Ionised Calcium</td>
<td>ionCa</td>
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<td>Parathyroid hormone</td>
<td>iPTH</td>
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<tr>
<td>Creatinine</td>
<td>Cr</td>
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<td>Fasting urine calcium excretion</td>
<td>urine CaE</td>
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<td>25 hydroxyvitamin D</td>
<td>Vit D</td>
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References