Need for early diagnosis of hyperparathyroidism

One in 500 patients in primary care have undiagnosed hyperparathyroidism, write Ann-Marie Mongan and John Lally

Primary hyperparathyroidism is the third most common endocrine condition after diabetes mellitus and thyroid dysfunction. The condition affects one in 700 individuals, and is three times more common in women. It primarily affects individuals in their 50s and 60s.

Parathyroid hormone is released by the four parathyroid glands. It regulates calcium metabolism. Increased levels of parathyroid hormone lead to hypercalcaemia via three main mechanisms: by increasing renal reabsorption of calcium; stimulating osteoclasts to resorb bone and move calcium into the extracellular space; and increasing renal production of calcitriol, which increases intestinal absorption of calcium and bone resorption.

Hyperparathyroidism is frequently asymptomatic but clinical manifestations may affect the renal, skeletal, gastrointestinal and neuromuscular systems. This constellation of symptoms is summed up by the mnemonic ‘stones, bones, abdominal moans and psychic groans’. Nephrolithiasis may occur but renal function remains stable. Elevated levels of parathyroid hormone cause bone demineralisation, which increases the risk of fracture and frequently leads to bone pain, arthritis, osteoporosis or osteitis fibrosa cystica. Gastrointestinal symptoms such as nausea, vomiting, anorexia and weight loss are commonly encountered. Non-specific neuromuscular symptoms such as impaired concentration and memory, confusion, lethargy, fatigue and muscle weakness are common presentations of this condition.

Normal calcium levels are 2.0mmol/l to 2.5mmol/l. Hypercalcaemia is considered mild if between 2.5mmol/l and 3mmol/l. As the concentration of calcium rises above 3.0mmol/l there is an increased likelihood of symptoms. Hypercalcaemia is considered life-threatening if above 3.5mmol/l, although exact values vary among laboratories. Elevated levels of serum calcium should be documented on two separate occasions to diagnose hypercalcaemia. The diagnostic work-up for hypercalcaemia is outlined in the algorithm in Figure 1.

General practice is well placed to pick up cases of hyperparathyroidism, be it in the case of incidental hypercalcaemia found on routine screening, osteoporosis or osteopaenia that is unexplained or resistant to recognised treatment, or osteoporotic fractures picked up incidentally on plane radiographs or following symptoms of fracture. It is essential to rule out excess parathyroid hormone as an underlying cause of hypercalcaemia because the subsequent aggressive osteoclastic activity and multisystemic manifestations may have devastating consequences, the indicated investigations will differ dramatically and the consequent treatment can be curative. This study was undertaken following investigations of five patients which were found in a normal general practice demographic, who had very different presentations and whose results all necessitated investigation into excess parathyroid hormone secretion.

Patient 1
A 72-year-old woman was seen by her GP at home as an emergency case in November 2005 with a two-day history of severe disabling left-sided mid-thoracic paraspinal pain which was worse on movement, on a background history of osteopaenia diagnosed on DXA scan two years previously. A diagnosis of traumatic thoracic vertebral collapse was made in the emergency department following cervical spine radiograph. After her return home her GP found her corrected serum calcium levels were elevated at 2.77mmol/l (normal range 2.15mmol/l to 2.55mmol/l). The diagnostic work-up was used to find the cause for her elevated calcium levels. Hyperparathyroidism was detected (parathyroid hormone level 138.0pg/ml, normal range 11-67pg/ml). In light of her hypercalcaemia, her diuretic medication and calcium supplement was stopped. A sestamibi scan done by the local radiologist revealed a probable parathyroid adenoma. An MIRP (minimally invasive radio-guided parathyroidectomy) followed and histology confirmed the diagnosis of a single parathyroid adenoma.

Patient 2
A 78-year-old woman presented to the general practice surgery in February 2006 with pain and stiffness in her lower back, hips and knees. A routine DXA scan had been carried out in June 2006 and showed osteoporosis. Despite treatment with calcium and vitamin D supplements and bisphosphonates, her repeat DXA failed to show an improvement in her bone mineral density. Parathyroid hormone and calcium levels were measured, showing a high normal corrected serum level of 2.41mmol/l (normal range 2.15mmol/l to 2.55mmol/l) and a raised parathyroid hormone level of 73pg/ml (normal range 11pg/ml-67pg/ml). She is currently awaiting a sestamibi scan to investigate her parathyroid glands for adenoma or other pathology.

Patient 3
A 75-year-old man presented to University College Hospital Galway in August 2005 as an elective admission for rehabilitation following a left cerebrovascular accident in March 2005. Routine biochemical investigations revealed an elevated corrected serum calcium level of 3.42mmol/l. His medications included Calcichew but he was not taking any thiazide diuretics, lithium, antacids, vitamin A analogues or supplements. He had no history of granulomatous disease,
endocrine disorders or malignancy. His family history was unremarkable. A 24-hour urinary calcium measurement showed an elevated urinary calcium level of 9.2mEq/24 hours (normal range 2.5mEq/24 hours to 7.5mEq/24 hours). His levels of parathyroid hormone were found to be elevated at 362mEq/ml (normal range 20mEq/ml-65mEq/ml). A sestamibi scan was negative. Surgical excision was performed in September 2005, which was curative with no complications.

**Patient 4**

A 44-year-old woman presented to the general practice surgery in February 2006 with hyperthermia and polydipsia. Routine biochemical investigations showed an elevated corrected serum calcium of 2.63mmol/l (normal range 2.15mmol/l to 2.55mmol/l). She had no other clinical features suggestive of hypercalcaemia, was on no medications and had no history of endocrine disorders, malignancy or granulomatous disease. Her father (patient three) had been diagnosed with hyperparathyroidism the previous year. Her parathyroid hormone levels were measured and found to be elevated at 87.3mEq/ml. A sestamibi scan in June 2006 confirmed the presence of a probable adenoma in the lower right pole of the thyroid. A minimally-invasive parathyroidectomy was scheduled.

**Patient 5**

A 68-year-old woman presented to the general practice surgery in November 2005, and routine biochemical investigations picked up an elevated corrected serum calcium level of 2.58mmol/l (normal range 2.15mmol/l to 2.55mmol/l). Of note was that she had a four-year history of osteopaenia, which was diagnosed on DXA scan, but no other clinical features of hypercalcaemia. She was known to have hypothyroidism and her medications included Ektroxin 100µg, and Calcichew D3 Forte, but no thiazide diuretics, lithium, antacids or vitamin A analogues or supplements. Other than her 30-year history of thyroid dysfunction she had no other endocrine disorders, malignancy or granulomatous disease. Family history was unremarkable. Thyroid function tests, renal function tests and parathyroid hormone assay were carried out. These tests revealed that she was euthyroid (on treatment) with normal kidney function and an elevated PTH level of 102.0pg/ml (normal range 11pg/ml-67 pg/ml). A sestamibi scan in May 2006 was negative, suggesting that four-gland hyperplasia was responsible for her hyperparathyroidism. A four-gland parathyroid exploration is planned.

**Underdiagnosis**

Parathyroid hormone-related conditions and malignant disease account for 90% of cases of hypercalcaemia. Less commonly, hypercalcaemia may be caused by granulomatous diseases such as sarcoidosis, endocrine disorders such as hyperthyroidism and adrenal insufficiency, medications such as thiazide diuretics or genetic conditions such as familial hypocalciuric hypercalcaemia. However, hypercalcaemia in conjunction with hyperparathyroidism is usually due to primary hyperparathyroidism.

As the above cases illustrate, hyperparathyroidism may present with osteoporotic fracture or osteoporosis or osteopaenia that is resistant to treatment. Calcium levels should be done on all such patients, and parathyroid hormone assays if then indicated. Hypercalcaemia detected on routine screening is the most common presentation of hyperparathyroidism. Forty percent of serum calcium is bound to plasma proteins such as albumin, and the remaining 60% is present as free ionised calcium. It is convenient to measure the free calcium directly, but the total calcium corrected for albumin level may be calculated by using various algorithms; for example: corrected calcium = [(40g/l – plasma albumin) x 0.02] + serum calcium. In all five cases outlined above, the albumin, phosphate and urea levels were normal, implicating primary and tertiary hyperparathyroidism as the most likely diagnoses. It is imperative to check parathyroid hormone levels in appropriate cases such as these. Parathyroid hormone assays measure biologically-active intact hormone from 5ml fasting samples, which must be kept on ice and delivered to the laboratory as soon as possible. Once the diagnosis of primary hyperparathyroidism is established biochemically, suitability for surgical management is determined on clinical grounds. Surgical excision is the treatment of choice with excellent cure rates and low incidence of complications.

Ultrasound or sestamibi scanning of the parathyroid gland is carried out as a guide once this decision has been made. Preoperative localisation with sestamibi scans has high sensitivity and specificity (> 90% and ~75%-83% respectively) and permits minimally-invasive radio-guided parathyroidectomy (MIRP) to be performed. However, open parathyroidectomy and four-gland exploration remains the procedure of choice for primary hyperparathyroidism.

Approximately one in 500 patients who are treated in primary care have undiagnosed hyperparathyroidism. Primary hyperparathyroidism is a very important and underdiagnosed cause of hypercalcaemia and therefore clinicians should have a high index of suspicion in patients with unexplained or unresponsive osteopaenia or osteoporosis and with all osteoporotic fractures, particularly in lower risk groups, (such as younger, male, active non-smokers with no family history of osteoporosis or fragility fractures). This case report will hopefully illustrate a commonly-underdiagnosed condition and possibly increase awareness of a potentially curable cause for the above symptoms and signs.

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References on request