

**Miriam Blackburn**

MBBS, BSc(Med), FRACP, is an endocrinologist in private practice, New South Wales. miriam\_blackburn@yahoo.com

**Terry Diamond**

FRACP, is Associate Professor, Department of Endocrinology, University of New South Wales, St George Hospital Campus, Kogarah, New South Wales.

# Primary hyperparathyroidism and familial hyperparathyroid syndromes

**BACKGROUND**

Ninety percent of cases of hypercalcaemia are due to primary hyperparathyroidism or hypercalcaemia of malignancy.

**OBJECTIVE**

This article outlines the diagnostic features of primary hyperparathyroidism and determines who would benefit from parathyroidectomy. It also aims to raise awareness of familial hyperparathyroid syndromes.

**DISCUSSION**

Diagnosis of primary hyperparathyroidism requires hypercalcaemia, elevated or inappropriately normal serum parathyroid hormone and a fractional urinary excretion of calcium greater than 0.02. Many patients benefit from parathyroidectomy, which has a high rate of cure.

**Serum parathyroid hormone (PTH) estimations are now frequently requested in the work up of patients with osteoporosis, renal and metabolic disorders. It is therefore important to differentiate between the various hyperparathyroid disorders, which can simply be classified into primary, secondary and tertiary hyperparathyroidism (Table 1).**

## Hypercalcaemia

Primary hyperparathyroidism and hypercalcaemia of malignancy are the most common causes of hypercalcaemia. Drug induced hypercalcaemia must also be considered when entertaining the diagnosis of primary hyperparathyroidism. Hypercalcaemia of malignancy is the commonest cause of hypercalcaemia in the hospital setting and can be differentiated from primary hyperparathyroidism by a suppressed serum PTH.

## Primary hyperparathyroidism

In general practice, primary hyperparathyroidism may occur as commonly as one in 2000 patients. This disorder is characterised by:

- an elevated serum calcium
- an elevated or inappropriately normal serum PTH, and
- frequently low serum phosphate due to renal phosphate wasting.

Most cases of primary hyperparathyroidism are sporadic, but there are also some familial hyperparathyroid syndromes.

It is important to differentiate familial hypocalcaemic hypercalcaemia (FHH) from primary hyperparathyroidism because primary hyperparathyroidism often requires parathyroidectomy and FHH does not. The following case studies and discussion highlight the important differentiating features to be considered when diagnosing primary hyperparathyroidism.

Primary hyperparathyroidism predominantly affects postmenopausal women. In 85% of cases it is caused by a single adenoma; 15% may have hyperplasia of multiple parathyroid glands. Parathyroid carcinoma is rare, affecting <0.5% of patients with hyperparathyroidism.<sup>1</sup> Risk factors for primary hyperparathyroidism include neck irradiation and lithium treatment. Classic presentations include: fractures, renal calculi, pancreatitis and neuropsychiatric disturbances; hence the traditional aide memoir 'bones, stones, abdominal moans and psychic groans'. With increased availability of serum calcium testing, these classic symptoms are now uncommon. Today, approximately 80% of patients with primary hyperparathyroidism are asymptomatic and are detected incidentally on routine biochemical assays.<sup>2</sup> Some patients may have subtle symptoms of fatigue and weakness that resolve after parathyroidectomy. Diagnosis is made by documenting hypercalcaemia in the presence of an elevated or inappropriately 'normal' serum PTH level, and a fractional urinary excretion of calcium >0.02.<sup>3</sup> The fractional excretion of calcium is calculated as (urine calcium x serum creatinine) ÷ (serum calcium x urine creatinine).

In order to eliminate the effects of fluctuations in dietary calcium intake, it is preferable to measure early morning urine calcium concurrently with an ionised serum calcium and PTH level after an overnight fast. A 24 hour urine calcium collection is useful to assess for hypercalciuria, which is a risk factor for renal calculi. Ionised serum calcium should be measured at least initially as it is more accurate than corrected calcium and eliminates rare cases of false positive elevations in serum calcium due to abnormal serum globulins.<sup>4</sup> The pathogenesis of primary hyperparathyroidism is not well understood. There is loss of normal feedback control of PTH by extracellular calcium and the cause is unknown.

### Treatment

Indications for surgery remain an area of controversy. According to the 2002 consensus statement from the Workshop on Asymptomatic Primary Hyperparathyroidism, indications for

### Case study 2

John, 65 years of age, has a history of hypertension, which is treated with ramipril. He complains of constipation. His serum total calcium level is 2.70 mmol/L (range 2.10–2.60), serum PTH 29.8 pmol/L (range 1–7) and fractional urinary excretion of calcium 0.023 (>0.01). A bone mineral density scan of the lumbar spine shows a density of 0.59 gm/cm<sup>2</sup> and a T score of –5.1. A parathyroid sestamibi scan demonstrates a single parathyroid adenoma. John has primary hyperparathyroidism complicated by osteoporosis. He proceeds to minimally invasive parathyroidectomy, which is curative. Bone mineral density substantially improves 12 months after successful parathyroid surgery.

surgery are patients who have complications or are at risk of developing complications (Table 2). Complications from primary hyperparathyroidism include renal calculi, peptic ulceration, acute pancreatitis, or fractures. Patients considered at risk of developing complications include those who have a serum calcium level of >2.85, hypercalciuria, reduced creatinine clearance, osteoporosis, and age less than 50 years. Patients who may be difficult to follow up longitudinally should also be recommended

for surgery.<sup>3</sup> Approximately 50% of patients meet surgical criteria for parathyroidectomy.<sup>5</sup> It is important that patients are referred to a surgeon expert in the field of parathyroid surgery, as their outcomes are excellent. Cure rates are 95% and complications of permanent hypoparathyroidism and recurrent laryngeal nerve palsy are uncommon.<sup>2</sup> General surgeons have higher complication and re-operation rates. Once the diagnosis of primary hyperparathyroidism is confirmed, a technetium parathyroid sestamibi scan can be used to determine the location of the parathyroid adenoma in preparation for minimally invasive parathyroid surgery. Minimally invasive parathyroid surgery is indicated in patients with primary hyperparathyroidism and a single parathyroid adenoma visualised on a preoperative technetium parathyroid sestamibi scan. The advantages of minimally invasive surgery include a smaller incision (<4 cm), shorter operation time, and the possibility of day only surgery (Figure 1, 2). A technetium parathyroid sestamibi scan has sensitivity of 90.7% and specificity of 98.8%.<sup>6</sup> A decrease of more than 50% of an intraoperative serum PTH assay confirms successful removal of the parathyroid adenoma.<sup>7</sup> Currently, the intraoperative PTH assay has limited availability in Australia. Patients who have persistent hyperparathyroidism after parathyroidectomy require detailed imaging techniques such as repeat parathyroid sestamibi scan, neck ultrasound, computerised tomography (CT) imaging, or occasionally, PTH venous sampling to localise abnormal parathyroids preoperatively. Impressive increases (12–14%) in bone mineral density have been demonstrated 10 years postparathyroidectomy.<sup>8</sup>

Patients managed medically need to ensure adequate hydration and mobilisation and consume the recommended daily allowance of calcium and vitamin D. Medications that may

**Table 1. Biochemical differences between primary, secondary and tertiary hyperparathyroidism**

	Primary hyperparathyroidism	Secondary hyperparathyroidism	Tertiary hyperparathyroidism
PTH	↑	↑	↑↑↑
Ca <sup>2+</sup>	↑ *	↓/N	↑
P <sub>04</sub> <sup>+</sup>	↓	↑/N	↑
Vitamin D	N/↓	↓↓↓	↓/N
Comments	In 85% a solitary parathyroid adenoma is present  Important differential diagnosis is FHH (see Table 3)	Causes include: • chronic renal failure • vitamin D deficiency	Caused by: • end stage renal failure

\* Differential diagnosis of hypercalcaemia includes drug induced (eg. lithium, thiazides) and hypercalcaemia of malignancy

### Case study 1

Ronald, 68 years of age, has a history of hypertension, multinodular goitre and bipolar depression. His medications are atenolol and lithium. His hypercalcaemia is discovered incidentally – he is asymptomatic. His serum total calcium is 2.86 mmol/L (range 2.10–2.60), serum PTH 14.7 pmol/L (range 1–7) and fractional urinary excretion of calcium 0.06 (>0.01). A bone mineral density scan showed a lumbar spine density of 1.05 g/cm<sup>2</sup> and a T score of –1.6. A parathyroid sestamibi scan was negative. Ronald’s psychiatrist recommended that his lithium should not be ceased because his bipolar disorder was well controlled on lithium. Considering the degree of hypercalcaemia and the inability to stop the precipitating agent, a decision was made to proceed to surgery. He had a total thyroidectomy and a three and two-thirds parathyroidectomy with one-third transplanted into the right sternocleidomastoid muscle. This was curative. Ronald had lithium induced hypercalcaemia.

**Table 2. Surgical treatment of primary hyperparathyroidism**

Parathyroidectomy recommended if:

- Serum Ca<sup>2+</sup> >2.85 mmol/L
- Hypercalciuria, urine Ca<sup>2+</sup> >10 mmol/day
- Creatinine clearance ≤70% of age matched normals
- Osteoporosis (bone density T score <-2.5)
- Less than 50 years of age
- Patients for whom medical surveillance is not possible or desirable

**Case study 3**

Mark, 28 years of age, is well and takes no regular medications. Mark's father and cousin have a history of mild hypercalcaemia. He presents complaining of polydipsia. On biochemical screening he is found to have hypercalcaemia. His serum total calcium is 2.87 mmol/L (range 2.10–2.60), serum PTH 6.9 pmol/L (range 1.5–7.6) and fractional urinary excretion of calcium 0.009 (>0.01). A bone mineral density scan shows a lumbar spine T score of 0.3 and a density of 1.275 g/cm<sup>2</sup>. A parathyroid sestamibi scan does not show an adenoma. Mark has familial hypocalciuric hypercalcaemia and does not require any treatment. Genetic counselling is arranged and the familial hypocalciuric hypercalcaemia mutation is confirmed in Mark, his father and a cousin.

exacerbate hypercalcaemia including calcium supplements, aluminium hydroxide, thiazides and lithium should be avoided. Elderly patients not suitable for parathyroidectomy can be treated with alendronate. Alendronate has been proven to increase bone mineral density by 4–6% but is unlikely to control hypercalcaemia.<sup>9</sup> Hormone therapy or raloxifene are alternatives to prevent bone loss in postmenopausal women who are unsuitable for surgery. Replacement of vitamin D in vitamin D deficient patients with co-existing primary hyperparathyroidism has been traditionally avoided due to the hypothetical risk of hypercalcaemia. There is early evidence that vitamin D replacement is safe in these patients and that it does not exacerbate hypercalcaemia.<sup>10</sup> Vitamin D deficiency appears to exacerbate disease activity in patients with primary hyperparathyroidism<sup>7</sup> (Figure 3). Intravenous bisphosphonates do not lead to sustained reductions in serum calcium levels. Calcimimetics increase the sensitivity of the calcium sensing receptor on the parathyroid cells to calcium. Cinacalcet, a calcimimetic, has been shown to normalise serum calcium but not to have any effect on bone mineral density. Medically treated patients need 6 monthly monitoring of their serum calcium, annual bone mineral densities and 24 hour urine calcium excretion. In one study at 10 year follow up of 52 asymptomatic patients

in their 50s with mild hypercalcaemia due to hyperparathyroidism, approximately one-quarter progressed to developing indications requiring parathyroidectomy.<sup>5</sup>

**Secondary and tertiary hyperparathyroidism**

Secondary hyperparathyroidism is characterised by an elevated serum PTH, but in contrast to primary hyperparathyroidism, the serum calcium is normal or low. Chronic renal failure and vitamin D deficiency are important causes of secondary hyperparathyroidism. End stage renal failure causes tertiary hyperparathyroidism, resulting in an elevated serum calcium, phosphate and PTH.

**Drug induced hypercalcaemia**

A thorough medication history is important when assessing hypercalcaemic patients. All patients on long term lithium therapy should have their serum calcium levels monitored as 5% will develop hypercalcaemia. Lithium induced hypercalcaemia is biochemically indistinguishable from primary hyperparathyroidism. In vivo and in vitro studies have demonstrated that lithium increases serum PTH and serum calcium and lowers urinary calcium excretion by decreasing the sensitivity of the calcium sensing receptors in the parathyroid gland and kidney to calcium.<sup>11</sup> Histopathological studies have been conflicting,



Figure 1. Demonstrates the standard 8 cm incision used for parathyroidectomy. This can be compared with Figure 2

Image courtesy Dr Chris Magarey



Figure 2. A 2 cm incision used in minimally invasive parathyroidectomy

Image courtesy Dr Chris Magarey

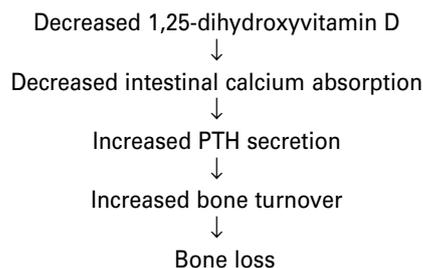


Figure 3. Vitamin D deficiency increases parathyroid hormone levels resulting in bone loss

some suggesting lithium unmasks a pre-existing parathyroid adenoma, others suggesting that lithium causes parathyroid gland hyperplasia.<sup>12</sup> Hypercalcaemia may persist long after cessation of lithium.<sup>1</sup> Thiazides can cause a mild elevation of serum calcium by increasing renal calcium reabsorption. Thiazides usually will only contribute to hypercalcaemia in the presence of a coexisting cause of hypercalcaemia such as primary hyperparathyroidism. If patients develop hypercalcaemia while taking thiazides or lithium, these drugs should be ceased if possible and the ionised serum calcium assessed again in 3 months.<sup>9</sup> If it is not possible to cease the lithium,

or if the hypercalcaemia persists long after cessation of the drug, it may be necessary to proceed to parathyroidectomy. The combination of a high intake of calcium and an alkali, calcium carbonate or antacids containing aluminium hydroxide, can lead to the development of milk-alkali syndrome. Milk-alkali syndrome presents with hypercalcaemia, metabolic alkalosis and renal impairment. It has become less common since the advent of improved therapies for peptic ulcer disease.

### Familial hypocalciuric hypercalcaemia

Familial hypocalciuric hypercalcaemia is an autosomal dominant condition, usually presenting as asymptomatic mild hypercalcaemia from birth. Serum PTH is normal or mildly increased, and patients may have a family history of hypercalcaemia. Fractional urinary excretion of calcium is important for distinguishing primary hyperparathyroidism from FHH (Table 3). Patients with FHH usually have a fractional urinary excretion of calcium <0.01 compared with

primary hyperparathyroid patients who usually have a fractional urinary excretion of calcium >0.02.<sup>3</sup> Familial hypocalciuric hypercalcaemia is a benign condition usually not requiring any treatment. To assist in making the diagnosis of FHH, family members need to be screened for mild hypercalcaemia and low fractional excretion of calcium. The FHH abnormal gene mutation can be assessed in the patient and in family members to confirm the diagnosis. Familial hypocalciuric hypercalcaemia is caused by an inactivating mutation of the calcium sensing receptor. The calcium sensing receptor regulates the sensitivity of the parathyroid cell to intracellular calcium. Patients with FHH have calcium sensing receptors less sensitive to inhibition by intracellular calcium. Subsequently, a higher set point of serum calcium is required to suppress PTH production. In the heterozygote form, it is a benign condition with an excellent prognosis, requiring no treatment. Rarely, the homozygote state causes life threatening neonatal hyperparathyroidism requiring total parathyroidectomy.

### Familial hyperparathyroidism

Familial hyperparathyroidism occurs in <5% of cases of primary hyperparathyroidism. Positive family history, presentation at a young age (<40 years) and multiple parathyroid gland hyperplasia are features suggesting that hyperparathyroidism may be a component of a familial syndrome.<sup>7</sup> Familial syndromes include:

- FHH
- familial hyperparathyroidism
- hyperparathyroidism jaw tumour syndrome
- multiple endocrine neoplasia (MEN) type I, and
- MEN type IIA (Table 4).

The existence of familial hyperparathyroidism as a disorder distinct from MEN I, MEN IIA, and hyperparathyroidism jaw tumour syndrome is debatable. Hyperparathyroidism jaw tumour syndrome is a rare syndrome characterised by hyperparathyroidism, renal tumours (Wilm tumours, polycystic kidney disease or renal harmartomas) and fibro-osseous tumours of the jaw. It is an autosomal dominant condition. Parathyroid carcinoma is more common in these patients.<sup>13</sup>

### Multiple endocrine neoplasia type I

Multiple endocrine neoplasia type I is an autosomal dominant condition with a high degree of penetrance. Patients with MEN usually present at a younger age than those with sporadic hyperparathyroidism. The features are hyperparathyroidism 95%, pituitary adenomas and pancreatic tumours. Pancreatic tumours may present as Zollinger Ellison syndrome in 70% of patients or insulinoma in 30%. Rarely the tumours secrete vasoactive intestinal peptide, prostaglandins, glucagon, pancreatic polypeptide, adrenocorticotrophic hormone (ACTH) or serotonin. Approximately 15–50% of

#### Case study 4

Susan, 54 years of age, has a history of osteoporosis treated with alendronate. She has no family history of hypercalcaemia or endocrine tumours. Her hypercalcaemia is an incidental finding on biochemical screening. She is asymptomatic. Her serum total calcium is 2.81 mmol/L (range 2.10–2.60), serum PTH 9.5 pmol/L (range 1–7) and fractional urinary excretion of calcium 0.026 (>0.01). Her bone mineral density scan shows a lumbar spine density of 1.08 g/cm<sup>2</sup> and a T score of –1.3. She has a negative parathyroid sestamibi scan. Total parathyroidectomy and autotransplantation of the parathyroid tissue into the forearm is undertaken. Histopathology shows three hyperplastic parathyroid glands. Two years later she represents with hyponatraemia secondary to cortisol and thyroxine deficiency. A pituitary magnetic resonance imaging (MRI) scan shows a 2 cm cystic pituitary adenoma with supracellar extension displacing the optic chiasm. Susan has a nonsecretory pituitary adenoma and subsequently undergoes transphenoidal hypophysectomy. She requires complete pituitary hormone therapy. Her fasting insulin, gastrin and VIP are normal. A CT of the abdomen does not demonstrate any pancreatic lesions. Susan has multiple endocrine neoplasia type I.

**Table 3. Distinguishing familial hypocalciuric hypercalcaemia from primary hyperparathyroidism**

	Primary hyperparathyroidism	Familial hypocalciuric hypercalcaemia
Family history	Negative*	Positive
Fractional excretion of Ca <sup>2+</sup>	≥0.02	<0.01
Symptoms of hypercalcaemia	Maybe symptomatic	Asymptomatic
Parathyroid sestamibi scan	Usually shows a single parathyroid adenoma	No abnormal parathyroid tissue demonstrable

\* With the exception of familial hyperparathyroid syndromes

**Table 4. Characteristics of familial hyperparathyroid syndromes**

Features	MEN I	MEN IIA	HPT-JT	Familial HPT	FHH
Hyperparathyroidism	✓	✓	✓	✓	✓
Pancreatic tumours	✓				
Pituitary adenomas	✓				
Medullary thyroid cancer		✓			
Phaeochromocytoma		✓			
Jaw and renal tumours			✓		
Inheritance	AD	AD	AD	AD, AR	AD
Gene mutated	Menin	RET proto-oncogene	Unknown	Unknown	Ca <sup>2+</sup> sensing receptor

MEN I = multiple endocrine neoplasia type I; MEN IIA = multiple endocrine neoplasia type IIA; HPT-JT = hyperparathyroidism jaw tumour syndrome; familial HPT = familial hyperparathyroidism; FHH = familial hypocalcaemic hypercalcaemia; AD = autosomal dominant; AR = autosomal recessive

MEN type I patients have pituitary adenomas and 30% have adrenal cortical hyperplasia. Multiple endocrine neoplasia type I is caused by a mutation to the MENIN gene on chromosome 11q13.<sup>13</sup> This mutation is an inactivating mutation of a tumour suppressor gene. There is usually hyperplasia of all four parathyroid glands requiring total parathyroidectomy and autotransplantation of parathyroid tissue to the forearm. Screening family members is not recommended as early detection does not reduce morbidity and mortality. This is in contrast to MEN type IIA where family screening (genetic testing) is recommended because it can result in a reduction in mortality. As primary hyperparathyroidism is the commonest presentation in MEN type I, family members are advised to have annual serum calcium and PTH estimations.

### Multiple endocrine neoplasia type IIA

Primary hyperparathyroidism is an almost universal feature in MEN type I. This is in contrast with MEN type IIA, where only 35% of patients develop primary hyperparathyroidism. Multiple endocrine neoplasia type IIA is characterised by medullary thyroid carcinoma, bilateral pheochromocytoma and hyperparathyroidism.<sup>13</sup> It is an autosomal dominant condition due to a mutation of the RET proto-oncogene – an activating mutation. If MEN type IIA is suspected, it is important to exclude pheochromocytoma before parathyroid surgery in order to prevent a possible life threatening pheochromocytoma crisis precipitated by anaesthesia. Family members need to be screened for the RET proto-oncogene mutation. Medullary thyroid carcinoma

is a life threatening condition that can be detected by a serum calcitonin assay. Accordingly, family members who have the RET proto-oncogene mutation require prophylactic thyroidectomy during childhood.

### Conclusion

The diagnosis of primary hyperparathyroidism requires hypercalcaemia, elevated or inappropriately normal serum PTH and a fractional urinary excretion of calcium >0.02. The clinical presentation of primary hyperparathyroidism has changed. Over the past 20 years the features of: 'bones, stones, abdominal moans and psychic groans' have been replaced by incidental biochemical hypercalcaemia discovered during routine evaluation or screening for osteoporosis. Approximately 50% of patients will meet surgical criteria for parathyroidectomy. Parathyroidectomy has a high rate of cure when performed by an endocrine surgeon, expert in parathyroid surgery. Five percent of cases of primary hyperparathyroidism are due to a familial cause. Features that flag the possibility of a familial cause are a positive family history, presentation at a young age (<40 years) and multiple parathyroid hyperplasia.

Familial causes include familial hypocalcaemic hypercalcaemia, MEN (type I and IIA), familial hyperparathyroidism and hyperparathyroidism jaw tumour syndrome. A fractional urinary excretion of calcium <0.01 in the context of a positive family history is suggestive of FHH. Unlike primary hyperparathyroidism, FHH is not cured by subtotal parathyroidectomy and unnecessary parathyroid surgery should be avoided.

Conflict of interest: none declared.

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**afp** CORRESPONDENCE email: [afp@racgp.org.au](mailto:afp@racgp.org.au)