Surgical management of parathyroid disease

Sheila Fraser

Abstract

Primary hyperparathyroidism is a common endocrine disorder caused by excessive PTH production by one or more parathyroid glands. The diagnosis is via biochemistry and surgery is the definitive treatment. All patients with symptomatic disease or evidence of end-organ damage should be offered surgery if possible. Imaging studies are used to plan surgical strategy. The majority of patients with primary hyperparathyroidism have a single parathyroid adenoma. Positive imaging studies allow patients to undergo minimally invasive surgery. Negative imaging does not rule out surgery and patients should be offered a traditional bilateral neck exploration. Secondary hyperparathyroidism is most commonly caused by renal failure. Medical management is the first line treatment, followed by parathyroidectomy in selected cases. Tertiary hyperparathyroidism is seen in patients with continued autonomous function of the parathyroid glands after removal of the underlying stimulus. It is commonly seen in renal transplant patients and parathyroidectomy has a role.

Keywords Hypercalcaemia; parathyroidectomy; primary hyperparathyroidism; secondary hyperparathyroidism; sestamibi; SPECT-CT; tertiary hyperparathyroidism

Embryology and development

An understanding of the embryology and development of the parathyroid glands is vital when considering parathyroid surgery. The parathyroids are the first endocrine glands to develop, usually during the 5th–6th weeks of gestation. There are two pairs of parathyroid glands – a superior and inferior pair. The superior glands arise from the dorsal aspect of the fourth branchial pouch, whilst the inferior develop from the dorsal aspect of the third branchial pouch. The pairs of parathyroid glands are usually symmetrically arranged on opposite sides of the neck.

The inferior parathyroid glands descend caudally and anteriorly along with the thymus. They have a longer decent than the superior glands and therefore have a more variable location. Over two-thirds of inferior parathyroid glands are found near the lower pole of the thyroid; however, they may lie anywhere along the line of the descent of the thymus, most commonly within the thyrothymic tract, but also within the superior mediastinum and rarely the carotid sheath.

The superior parathyroid glands descend with the thyroid, following the migration of the ultimobranchial bodies. Due to the shorter migration the superior parathyroids tend to show less anatomical variation and are usually found just outside the thyroid's fibrous capsule, more posterior and medial than the inferior parathyroid glands. The majority are located just above the junction of the inferior thyroid artery and recurrent laryngeal nerve (RLN). Ectopic superior parathyroid glands are often located in a para-oesophageal or retro-oesophageal position.

Around 20% of parathyroid glands lie in an ectopic position and this is a common cause of failed parathyroid surgery. A small number, up to 4%, have been found completely within the thyroid. This is likely due to fusion of a superior parathyroid gland with the ultimobranchial bodies during embryological development. Supernumerary glands have been quoted as present in up to 13% of patients on random autopsies, frequently seen in the thymus or the along the embryological descent of the inferior parathyroid glands. Supernumerary parathyroids are thought to be due to tissue fragmentation during migration of the glands, rather than true extra glands. Furthermore, about 3% patients are thought to have an absent parathyroid gland.

Function of the parathyroid glands

Over 99% calcium in the body is located within the bones, with only 1% in other tissues and fluids. Serum calcium concentration is kept in a very tight range. The key regulator of calcium homeostasis is parathyroid hormone (PTH), produced by the chief cells of the parathyroid glands. PTH is released in response to small drops in serum calcium levels that activate calcium-sensing receptors on the chief cells. Increased PTH levels raise serum calcium levels by instigating additional reabsorption of calcium by the renal tubules and stimulate osteoclasts causing bone resorption. PTH also activates the enzyme 1-α-hydroxylase in the proximal tubules of the kidneys, causing conversion of 25-hydroxyvitamin D to its active metabolite 1,25-dihydroxyvitamin D stimulating absorption of calcium and phosphate in the gastrointestinal tract.

Definition of hyperparathyroidism

Hyperparathyroidism is split into primary, secondary and tertiary hyperparathyroidism.

Primary hyperparathyroidism (PHPT)

One or more parathyroid glands are overactive, causing hypercalcaemia due to inappropriately high PTH levels. PHPT is a biochemical diagnosis with raised calcium and normal or high PTH levels. Normal PTH levels on the background of hypercalcaemia are considered abnormal and in keeping with primary hyperparathyroidism, as PTH secretion should be suppressed with high serum calcium levels. Primary hyperparathyroidism is associated with normal or high urinary calcium excretion.

Incidence and aetiology

Primary hyperparathyroidism is the third most common endocrine disorder, with an annual incidence of 1–4 per 100 people affected in the general population. The frequency increases with age, and is the highest in post-menopausal women with a 3–4:1 ratio of women to men. Prior exposure to ionizing irradiation and lithium therapy are both known risk factors for PHPT. Long-term lithium treatment is associated with PHPT in up to 15% people with an increased incidence of multi-gland disease.

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Eighty-five to ninety per cent of patients diagnosed with PHPT have a single adenoma, whilst 3% have double adenomas. Multigland disease (four-gland hyperplasia) occurs in 10% patients and parathyroid carcinoma is a rare cause in less than 1% of patients.

The majority of cases of PHPT are sporadic, but less than 10% are associated with familial inherited syndromes. Genetic conditions include multiple endocrine neoplasia (MEN) type 1 and 2a, familial isolated primary hyperparathyroidism, and hyperparathyroidism-jaw tumour syndrome (HPT-JT). Around 15% patients under 40 presenting with apparently sporadic PHPT have an underlying genetic syndrome and young patients should be referred for genetic counselling and screening.

The prevalence of PHPT varies in each syndrome. Hyperparathyroidism is usually the first endocrinopathy in patients with MEN1 to be diagnosed and occurs in up to 90% of patients. In MEN2a, around 35% patients develop PHPT, with MTC and phaeochromocytomas being more frequently diagnosed. Both MEN1 and MEN2a are autosomal dominant conditions with MEN1 caused by inactivating mutations of the MEN1 gene and MEN2a due to activating mutations of the RET oncogene.

Hyperparathyroidism-jaw tumour syndrome (HPT-JT) is an autosomal dominant disorder with mutations in the CDC73 (also called HRPT2) gene. It is characterized by parathyroid tumours (of which 10–15% are parathyroid carcinomas), and fibro-osseous tumours of the jawbone. HPT-JT patients are also prone to renal abnormalities, including Wilm's tumours, hamartomas and polycystic disease.

Familial isolated PHPT is an autosomal dominant condition that may represent an early stage of either MEN1 or HPT-JT syndromes, with mutations seen in both the MEN1 and CDC73 genes. Alternatively, it is could be due to a distinct variant of the above genes, causing a predisposition to only PHPT.[1]

It is important to rule out familial hypocalciuric hypercalcaemia (FHH) during investigations for PHPT. FHH is an autosomal dominant disorder usually due to inactivating mutations in the gene for the calcium-sensing receptor (CaSR). This should be considered in young patients with mildly elevated calcium and PTH levels and low urinary calcium levels. Low vitamin D levels can interfere with 24 hour urinary calcium levels, but this can be corrected and urine calcium rechecked if there are any concerns. Confirmation is via calcium/creatinine urinary clearance ration (CCUCR) and if this is less than 1% patients should be referred to an endocrinologist or geneticist rather being planned for surgery.

Indications for surgery (Table 1)

Over the past few decades PHPT has changed from a condition that presented symptomatically to one that is often asymptomatic and discovered on routine blood tests.

Surgery remains the only definitive treatment for PHPT. All symptomatic patients with a biochemical diagnosis of PHPT should be offered surgery.

All patients with PHPT should undergo a renal ultrasound and DEXA bone scan to screen for asymptomatic renal calculi and a reduction in bone density.

PHPT can additionally produce a range of symptoms, including neuropsychiatric, cognitive, musculoskeletal, and gastrointestinal complaints. These are usually a direct result of hypercalcaemia and can range from mild and non-specific to severe. Symptoms should be discussed in detail as symptoms often resolve post-parathyroidectomy and are another indication for surgical intervention.[2]

Current indications for parathyroid surgery

Symptomatic patients	Asymptomatic patients
Hypercalcaemic crisis	Age <50 years
Renal calculi	Serum calcium level >0.25 mmol/L above the upper limit of normal
Fragility fractures	Creatinine clearance reduced to <60 ml/min
Osteoporosis	T-score <−2.5 at any site
Any suspicion of parathyroid cancer	Silent renal calculi on imaging

Table 1

There remains debate about whether or when to intervene in patients with mild asymptomatic PHPT with no end-organ damage, who do not fulfil the criteria above for surgery. Studies have demonstrated that there is a slow decline in bone mineral density over several years and that this improves after surgery. Increased cardiovascular morbidity has also been recognized in patients with apparent asymptomatic hyperparathyroidism; however, data on potential cardiovascular manifestations are still not yet definitive. Many endocrinologists prefer conservative management and continue monitoring until end-organ damage is evident.[3]

When patients do not fulfil the criteria for surgery or are unfit or unwilling to proceed they should be regularly monitored (Table 2). The current protocol for follow up is that suggested by the 2009 National Institute of Health Consensus Conference.

Medical treatment for PHPT

Patients with mild asymptomatic PHPT should be monitored as advised above. Medical management can be considered in patients with contraindications to surgery and significant primary or persistent hyperparathyroidism.

Calcimimetics, for example cinacalcet, can lower serum calcium and PTH values. Cinacalcet is an agonist of the calcium-sensing receptor, changing the structural configuration and increasing sensitivity to serum calcium, therefore reducing PTH and calcium levels. However, many patients cannot tolerate cinacalcet and it does not affect the underlying bone density. It is currently only recommended in patients with PHPT who are unable to tolerate surgery.

Bisphosphonates will reduce PTH-driven bone resorption, so increasing bone density but no reduction in serum calcium levels has been observed. PTH levels may actually increase with bisphosphonate treatment.

Monitoring of patients who do not undergo parathyroid surgery

Investigation	Frequency
Serum calcium	Annually
Serum creatinine	Annually
Bone density	Every 2–3 years

Table 2