Current management of parathyroid tumours

Most parathyroid tumours are benign causing primary hyperparathyroidism. The number of patients diagnosed has risen significantly with routine biochemical testing. This review discusses the management of these and other parathyroid tumours.

Parathyroid tumours lead to increased secretion of parathyroid hormone. Previously this was only detected when calcium levels became very high and patients became symptomatic. Since the introduction of the AutoAnalyzer in the 1970s blood samples are routinely assessed for calcium levels using automated serum analysis. This has resulted in a significant increase in the numbers of patients identified with hyperparathyroidism, particularly patients with mild symptoms or those that are asymptomatic. The benefits and risks of treatment must then be evaluated, especially in the asymptomatic patient, to decide a treatment plan.

The vast majority of parathyroid tumours are benign. However, hyperparathyroidism is not always caused by a parathyroid tumour. The other causes of hyperparathyroidism will be discussed further including diagnoses and treatment. Much less commonly parathyroid tumours may be malignant. The rarity of this disease makes evidence-based management more difficult but will be reviewed.

Primary hyperparathyroidism

This is caused by neoplastic or hyperplastic growth of parathyroid parenchymal cells leading to increased secretion of parathyroid hormone; 80% of patients have a single adenoma. As it is an isolated parathyroid abnormality it is not usually associated with other biochemical abnormalities. It is more common in older age; the incidence of disease by the sixth decade is approximately 1 in 500 in women and 1 in 1000 in men (Heath et al, 1980).

Presentation

Symptomatic patients present with the features of hypercalcaemia (*Table 1*). However, 80% of patients are identified incidentally on biochemical screening. Diagnosis may also occur while screening for osteopenia, osteoporosis or nephrolithiasis.

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Diagnosis

Hypercalcaemia with a normal or elevated parathyroid hormone level is diagnostic of primary hyperparathyroidism. However, 10–20% of patients may be normocalcaemic at least on one testing. This may be a result of two factors: intermittent secretion by the parathyroids and additional vitamin D deficiency. Vitamin D replacement and repeat calcium checks will identify these patients (LoCascio et al, 1985).

Other useful tests include serum phosphate levels, which are usually at the lower end of the normal range, and serum creatinine, as chronic hypercalcaemia can lead to renal impairment. 24-hour urinary calcium levels and bone densitometry evaluation are useful in decision making regarding management.

Treatment

Primary hyperparathyroidism may be managed conservatively, medically or surgically, although surgery is the only curative modality. In symptomatic patients, the decision to treat surgically is often straightforward as long as the patient is fit. If not, with concordant imaging suggesting a solitary parathyroid adenoma, local anaesthetic resection is feasible.

Table 1. Features of hypercalcaemia

Muscle weakness
Muscle and bone aches and pains
Depression
Constipation
Tiredness
Peptic ulceration
Pancreatitis
Renal impairment
Nephrogenic diabetes insipidus
Nephrolithiasis
Shortened QT interval
Band keratopathy
Thirst and polyuria

As currently the majority of newly diagnosed patients are asymptomatic, conservative management with clinical observation is an option. Patients are encouraged to remain well hydrated. Thiazide diuretics are contraindicated as they reduce calcium excretion. Avoidance of calcium in the diet is unnecessary as long as the serum vitamin D levels are not elevated since this does not alter urinary calcium excretion (Locker et al, 1997).

Medical treatment includes various drugs used to control calcium and parathyroid hormone levels. Most frequently bisphosphonates are prescribed as first line management; they decrease bone turnover and also decrease serum and urinary calcium levels. More recently, calcimimetic drugs such as the second generation cinacalcet have gained in popularity, but are expensive. They rapidly bring about a decrease in serum parathyroid hormone levels. National Institute for Health and Clinical Excellence (2007) guidelines suggest they should be used only in refractory secondary hyperparathyroidism when surgical parathyroidectomy is contraindicated. They can also be used in primary hyperparathyroidism where surgery is contraindicated and in parathyroid cancer. Oestrogen replacement therapy is also used in postmenopausal women with mild hyperparathyroidism to protect bone density in both the lumbar vertebrae and the femoral neck (Orr-Walker et al, 2000).

Up to a quarter of patients initially judged as asymptomatic deteriorate over a 10-year period and eventually require surgery (Silverberg et al, 1999). Consequently the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases recommend parathyroidectomy for asymptomatic patients in specific circumstances (*Table 2*) (Bilezikian and Potts, 2002). With this in mind, if the decision to adopt a watchful waiting approach is taken, annual serum calcium, parathyroid hormone and renal function estimation, with interval bone densitometry evaluation, is advisable so that any deterioration is picked up early.

Secondary hyperparathyroidism

This is not a true parathyroid tumour as it reflects other biochemical influences stimulating the gland. Low levels of calcium and/or vitamin D lead to raised parathyroid hormone levels; this results in parathyroid cell proliferation and gland enlargement. When the stimulus is removed the parathyroid glands should return to their normal state.

Secondary hyperparathyroidism can have a variety of causes, the most recognized being chronic renal failure. Other causes include vitamin D deficiency, lithium therapy, intestinal malabsorption syndromes with inadequate absorption of vitamin D and calcium, heart failure, hypertension and long-term total parenteral nutrition (Goodman et al, 2000).

Diagnosis

Raised parathyroid hormone levels in the presence of normal or mildly elevated calcium and/or low vitamin D levels (below normal range or within the lower third of the normal range).

Treatment

Secondary hyperparathyroidism patients can be treated by removal of the stimulus or medically with phosphate binders, calcitriol and calcium supplementation. Medical treatment fails in about 5% of patients who become unsuppressible or autonomous (tertiary hyperparathyroidism) requiring parathyroidectomy (Pasieka and Parsons, 2000). This is usually total parathyroidectomy with or without autotransplantation of tissue into the forearm or strap muscles, sometimes with cryopreservation of parathyroid tissue for subsequent grafting if the initial transplant fails. Surgery for lithium-induced secondary or tertiary hyperparathyroidism should include bilateral neck dissection because of the relatively high frequency of multigland involvement (Hundley et al, 2005).

Tertiary hyperparathyroidism

In chronic secondary hyperparathyroidism, growth of a hyperplastic gland may become autonomous. In these cases even once the chronic stimulus has been removed the gland remains hyperplastic or becomes frankly adenomatous. This most commonly occurs in chronic renal failure but can occur in any cause of secondary hyperparathyroidism.

Diagnosis

In chronic kidney disease, tertiary hyperparathyroidism is present if the hyperparathyroidism is not reversed by a renal transplant and normalisation of kidney function. It is also considered present in dialysis patients when the calcium/phosphate product exceeds 5 or parathyroid hormone exceeds 100 pmol/litre (normal range 1.2–5.8 pmol/litre). This is the level where calcium deposition in tissues is more likely to occur (calcinosis cutis).

Table 2. National Institutes of Health indications for parathyroidectomy in asymptomatic primary hyperparathyroidism

Less than 50 years old
Unable to be effectively followed up
Serum calcium >1.0 mg/dl above the normal range
Urinary calcium >400 mg/24hr
30% decrease in renal function
Complications of hyperparathyroidism: nephrocalcinosis, osteoporosis (T-score <2.5 standard deviation at lumbar spine, hip or wrist)
Severe psychoneurological disorder

Treatment

As with secondary hyperparathyroidism surgery usually involves total parathyroidectomy with or without autotransplantation.

Hereditary hyperparathyroidism

This category includes seven groups shown in *Table 3*.

Non-neoplastic hereditary hyperparathyroidism

Familial hypercalcaemic hypocalciuria, autosomal dominant mild hyperparathyroidism (familial hypercalcaemia with hypercalcuria) and neonatal severe hyperparathyroidism are caused by mutations in the calcium receptor set-point gene. Because of the altered set-point, all three conditions have hyperparathyroidism at birth. Familial hypercalcaemic hypocalciuria is heterozygous and associated with mild elevations in serum calcium with virtually no morbidity. Autosomal dominant mild hyperparathyroidism produces higher levels of hypercalcaemia and is associated with hypercalcuria and in some cases renal stones. Neonatal severe hyperparathyroidism is homozygous and causes life-threatening hypercalcaemia requiring urgent intervention in the neonatal period.

Treatment

Familial hypercalcaemic hypocalciuria does not require treatment. Autosomal dominant mild hyperparathyroidism and neonatal severe hyperparathyroidism are treated with total parathyroidectomy.

Neoplastic hereditary hyperparathyroidism

The four other familial conditions are neoplastic and associated with an early age of onset for hyperparathyroidism (average age 25–35 years). Patients with multiple endocrine neoplasia type 1 typically present with hypercalcaemia caused by multi-gland hyperparathyroidism but may also develop pancreatic and foregut carcinoids and pituitary tumours. Multiple endocrine neoplasia type 2a is associated with medullary thyroid carcinoma and phaeochromo-cytoma. Hyperparathyroidism-jaw syndrome is a rare familial syndrome with severe hypercalcaemia associated with a higher incidence of parathyroid carcinoma (15%). Familial-isolated hyperparathyroidism combines several diagnoses and may have single or multiple gland disease.

Table 3. Types of hereditary hyperparathyroidism

Familial hypercalcaemic hypocalciuria
Autosomal dominant mild hyperparathyroidism (familial hypercalcaemia with hypercalcuria)
Neonatal severe hyperparathyroidism
Multiple endocrine neoplasia type 1
Multiple endocrine neoplasia type 2a
Hyperparathyroidism-jaw syndrome
Familial-isolated hyperparathyroidism

Treatment

Some of the neoplastic hereditary hyperparathyroidism conditions can respond to less than total parathyroidectomy although long-term control is variable. In multiple endocrine neoplasia type 1 anything less than a subtotal parathyroidectomy is associated with high recurrence rates and many authors advocate total parathyroidectomy with autotransplantation. In multiple endocrine neoplasia type 2a hypercalcaemia is usually mild and may require no treatment or simply removal of enlarged gland(s). Hyperparathyroidism-jaw syndrome requires total parathyroidectomy. The surgical treatment of familial-isolated hyperparathyroidism varies depending on the clinical findings.

Parathyroid carcinoma

Parathyroid carcinoma is extremely rare, comprising less than 1% of all hyperparathyroidism presentations. Suspicion should be raised if the calcium and parathyroid hormone levels are particularly high. In contrast to benign adenomata the tumour is often palpable (in 45% of cases in the Mayo series; Wynne et al, 1992). In addition, patients with parathyroid carcinoma tend to be more symptomatic, having a high incidence of renal dysfunction, osteoporosis and gastrointestinal symptoms (Chiofalo et al, 2005). It seems that most cases of parathyroid carcinoma are idiopathic, although there are some reports suggesting that its incidence is raised in those who have undergone neck irradiation in the distant past.

Treatment

The only curative treatment modality is surgery aiming for en-bloc resection of the tumour mass together with the ipsilateral thyroid lobe, and all other involved structures therefore avoiding transgression of the tumour capsule. However, it is usually not possible to obtain a preoperative diagnosis and therefore for optimal outcome intraoperative recognition is of the utmost importance. As a consequence many patients require revision surgeries (60% in the Mayo series).

Traditionally parathyroid carcinoma is seen as radioresistant, but some retrospective data appear to suggest it is an effective treatment modality (Busaidy et al, 2004). The role of postoperative radiotherapy is therefore not clear. Adjuvant chemotherapy seems to confer short lived, if any, benefit (Rodgers and Perrier, 2006). Ultimately, patients who die of parathyroid carcinoma do so from the effects of hypercalcaemia. Local recurrences should therefore be treated by further surgical resection, and bisphosphonates and calcimimetics are useful for symptomatic control.

Surgical technique

The majority of parathyroid surgery is performed for primary hyperparathyroidism. This can be either targeted to one gland or four gland exploration, where each gland is examined. Targeted surgery can be minimally invasive and can be performed under local anaesthetic, but this approach is only suitable in primary hyperparathyroidism with a solitary adenoma which has been identified on two concurrent scans (ultrasound and scintigraphy). The benefits of targeted surgery mean a smaller incision with shorter operating time. The drawbacks are that of additional time and cost spent on two separate preoperative investigations which may prove not to be useful. Total parathyroidectomy is used for secondary and tertiary hyperparathyroidism in addition to parathyroid carcinoma and some of the hereditary hyperparathyroidism syndromes. The technique is the same as for four gland exploration but each gland is removed.

Four gland exploration

A horizontal incision is made midway between the cricoid cartilage and the jugular notch. This extends though platysma and a myocutaneous flap is raised. The parathyroids can then be approached either from medial or lateral to the strap muscles. The lateral approach is used more frequently in revision surgery. When approaching medially the linea alba is identified and the strap muscles separated. The thyroid is retracted medially and the strap muscles laterally. The fine fibrous bands between the thyroid and surrounding structures are divided. The thyroid is mobilized onto the trachea and held with a stay suture. When approaching laterally the fascia between sternomastoid and the straps is divided to reveal the carotid sheath. The sternomastoid is retracted laterally and the thyroid medially.

Searching for the superior gland

The inferior thyroid artery and recurrent laryngeal nerves are identified. The posterior surface of the superior pole of the thyroid is examined, most superior parathyroids are found within 1 cm of the cricothyroid joint.

Searching for the inferior gland

The inferior pole of the thyroid is mobilized and the area of the thyro-thymic tract examined. The inferior gland normally lies on or just below the inferior pole of the thyroid lobe.

When a parathyroid is found it is examined. If normal it is marked with a ligaclip. If it is enlarged or abnormal it is removed. It is often appropriate to submit a biopsy of a normal gland for histological diagnosis at the same time. The process is then repeated on the other side. If no abnormal gland is found then the thymus, thyroid and carotid sheath should be carefully examined.

Targeted parathyroidectomy

Minimal access techniques which may be laparoscopic, video assisted or without endoscopic enhancement normally depend on accurate preoperative localization. Unilateral explorations and single gland targeted excisions through incisions of 1.5 cm are feasible. In some institutions, minimal access video-assisted parathyroidectomy enables a bilateral four gland exploration through a single medial horizontal 1.5 cm incision (Miccoli et al, 2004). These advances have paved the way to local anaesthetic outpatient procedures producing comparable results to the traditional four gland technique (Udelsman, 2002), although patient selection criteria must be firmly established for such cases and patient suitability varies from 60–96% depending on the reporting institution (Inabnet et al, 1999; Rubello et al, 2005).

Complications of surgery

The main risks of surgery are bleeding or haematoma, damage to the recurrent laryngeal nerve causing vocal cord paralysis and failure to cure hyperparathyroidism.

Surgical failure and reoperative parathyroid surgery

The reasons for surgical failure in order of frequency are inadequate cervical exploration, failure to diagnose or adequately resect multigland disease, gland ectopia and the wrong diagnosis. It is vital to maximize surgical success rates at the first operation because the risks of complications increase with further surgery and the risks of success decrease, with revision success rates ranging from 65–98% (Shen et al, 1996; Low and Katz, 1998).

When failure occurs other possible diagnoses, in particular familial hypercalcaemic hypocalciuria, pseudohyperparathyroidism and sarcoidosis must be excluded. Second, the requirement for revision surgery must be re-evaluated and its necessity reconfirmed – patients may opt for watchful waiting. Before revision surgery pre-operative localization should be repeated and the histological specimens and operative notes from the first exploration should be examined, as these will often help in pointing to the likely location of the missing gland.

Localization techniques

When planning targeted parathyroidectomy, the surgeon will normally only proceed if a technetium ^{99m}Tc sestamibi scan is concordant with a high resolution ultrasound scan in localizing the parathyroid tumour (Inabnet et al, 1999).

Scintigraphy

Technetium ^{99m}Tc sestamibi with either a subtraction technique using radioiodine (^{123}I) or used alone in a 'double-phase scan' where the scan is repeated at 2–3 hours gives the best results (Thulé et al, 1994). The double-phase method relies on the differential washout rate of sestamibi from parathyroid tissue compared to thyroid tissue because of the high metabolic rate of the parathy-

roids, particularly when adenomatous. Of the two technetium techniques, the subtraction technique is currently superior, localizing solitary adenomata in 95% of cases and multigland disease in 80% (Hindié et al, 1997). Scintigraphy may be less effective in ectopic glands as the localization of abnormal glands may be hampered by overlying structures, particularly when the lesion is below the clavicles.

Ultrasonography

Ultrasonography results are operator dependent, but in the best hands solitary adenomas can be identified in 93% of cases using colour Doppler (Reeder et al, 2002). It is of limited value when glands are ectopic, particularly when they are located in the mediastinum.

Ectopic glands

If scintigraphy and ultrasonography do not identify the adenoma, particularly in revision surgery three dimensional imaging techniques such as magnetic resonance imaging and highly selective venous sampling, single photon emission computed tomography or positron emission tomography with either (18F)-fluoro-2-deoxy-D-glucose or (11C)-methionine are useful (Beggs and Hain, 2005).

Gamma probe

Parathyroid localization may be further enhanced intraoperatively by the use of the gamma probe. First described as a technique useful in both gland ectopia and hyperplasia in 1995, it depends on the identification by a gamma probe of a radioisotope injected preoperatively and selectively concentrated within parathyroid tissue (Martinez et al, 1995). The procedure depends on strict timing between radioisotope injection and time of surgery, and although not in widespread use has certainly gained some acceptance in minimally invasive parathyroidectomy (Caudle et al, 2006).

KEY POINTS

- Parathyroid tumours are benign in approximately 99% of cases.
- Parathyroid tumours are the commonest cause of hypercalcaemia. The second commonest cause is disseminated malignancy which should always be considered.
- Primary hyperparathyroidism is diagnosed in relatively asymptomatic patients in 75% of cases and there are well-recognized guidelines for when to advise surgery in these patients.
- Primary hyperparathyroidism is common in patients over the age of 60 years, but occurs in all age groups.
- Renal failure is the most recognized, but not the only, cause of secondary hyperparathyroidism.
- Tertiary hyperparathyroidism is the continuation of hyperparathyroidism once the extraneous stimulus causing secondary hyperparathyroidism has been removed.

Methylene blue

This involves the preoperative intravenous administration of methylene blue 5 mg/kg in saline (Dudley, 1971). The dye is preferentially taken up by the parathyroids, particularly when adenomatous or hyperplastic hence making their identification easier. Again timing of infusion to surgery is crucial. The patient's skin will have a blue hue for a few days following surgery, and there may be some nausea.

Conclusions

Primary hyperparathyroidism represents the majority of causes of hyperparathyroidism. Owing to advances in serum analysis many more patients are being identified, the majority of whom are asymptomatic. The only curative treatment is surgery. National Institutes for Health guidelines highlight asymptomatic patients for whom surgery is recommended. All others should have serial monitoring as they may require surgery at a later date.

Secondary and tertiary hyperparathyroidism are a result of other biochemical changes and may respond to medical interventions. Uncontrolled disease requires parathyroid surgery. Hereditary hyperparathyroidism is rare and some forms are associated with other malignancies. Management can be complex and often involves surgery. Parathyroid carcinoma is rare, representing less than 1% of cases of hyperparathyroidism. Surgery is the only curative treatment. Owing to the low incidence of this disease further research is needed to determine the best adjuvant management

Parathyroid surgery may involve four gland exploration to identify the abnormal gland. Alternatively it can be targeted requiring preoperative localization using modalities such as ultrasonography and scintigraphy. Recent advances have led to increasing numbers of operations being performed under local anaesthetic in addition to minimally invasive, video assisted and laparoscopic operations. This will hopefully reduce morbidity, hospital stay and costs of treatment although success and complication rates will need to be carefully assessed. **BJHM**

Conflict of interest: none.

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