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The parathyroid glands and anaesthesia

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Introduction

A parathyroid adenoma causing primary hyperparathyroidism was successfully resected for the first time in Vienna in 1925.[1] Primary hyperparathyroidism is now considered the third most common endocrine disorder[2] and many patients will present for surgical removal of one or more of their parathyroid glands. This article presents a review of parathyroid gland anatomy, physiology and dysfunction, as well as the anaesthetic management of patients presenting for parathyroidectomy.

Anatomy

Most humans have two pairs of parathyroid glands. The two superior glands are usually embedded in the posterior borders of the superior poles of the thyroid gland. The inferior glands have a more variable location due to their embryonic origin and development. They are most commonly found close to the inferior thyroid poles, anterior to the recurrent laryngeal nerves, but may descend together with the thymus into the mediastinum.[3-6] The individual glands measure about 3x6x2 mm.[3] They have an abundant blood supply from the inferior thyroid arteries and their venous and lymphatic drainage is shared with that of the thyroid glands.[7] Histologically, the glands consist predominantly of chief cells, which produce and secrete parathyroid hormone (PTH). The function of the oxyphil cells is unknown.[3]

Physiology

Human PTH regulates calcium homeostasis and is essential for life. Many physiologic processes such as cell signalling, muscle contraction, propagation of action potentials, coagulation and regulation of cell growth are dependent on the tight control of ionised calcium. Two other hormones; vitamin D and calcitonin, also contribute to calcium homeostasis. PTH exerts its effect on three organs: kidneys, bones and intestines.[1-3,7]

Effects of PTH on the kidneys:

PTH increases calcium reabsorption from the ascending loop of Hendle, the distal convoluted tubule and collecting duct. The hypercalcaemia caused by PTH excess, however, overwhelms these reabsorption mechanisms, resulting in urinary calcium losses.[1,3,6]

PTH inhibits sodium-dependent phosphate absorption in the proximal and distal tubules. Furthermore, inhibition of sodium reabsorption proximally results in an increased sodium load in the distal tubule. The net effect of this is an increased free water clearance.[6]

PTH inhibits bicarbonate reabsorption in the proximal renal tubule. This explains the renal tubular acidosis and hyperchloraemia seen in primary hyperparathyroidism.[6]

PTH also increases the activity of renal vitamin D 1α-hydroxylase, which converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (Vitamin D3).[1,3,6]

Effects of PTH on bone

The effects of PTH on bone are complex (both anabolic and catabolic) and occur as different phases. PTH excess, however, increases osteoclast-mediated calcium and phosphate resorption from bone. 1,25-dihydroxycholecalciferol also enhances bone resorption, but calcitonin opposes it.[1,6]

Effects of PTH on the intestine

PTH indirectly increases the absorption of calcium from the intestine through its effect on the activity of renal vitamin D 1α-hydroxylase.[3]

Regulation of PTH secretion

The calcium-sensing receptor (CaSR) is found on the cell membranes of many tissues. It is a G-protein coupled receptor that responds to changes in circulating ionised calcium. In the parathyroid glands, it sits on the surface of the chief cells and regulates calcium homeostasis via a negative feedback mechanism. Once activated, the CaSR inhibits PTH secretion and calcium is deposited in bone. When the circulating ionised calcium level is low, PTH is secreted and calcium is mobilised from bone.

1,25-dihydroxycholecalciferol directly decreases the transcription of PTH genes. Serum phosphate lowers circulating calcium and inhibits the formation of 1,25-dihydroxycholecalciferol and thereby stimulates PTH secretion. Changes in circulating magnesium concentrations, outside the normal physiological range, have similar effects to changes in circulating calcium concentrations.[3,6]

Calcium homeostasis

More than 99% of total body calcium is stored in skeletal bone. Extra and intracellular fluid only contains about 70 mmol of calcium. In the extracellular fluid, calcium exists in three forms: ionized cations (45%), calcium complexed to phosphate and citrate (5%) and protein-bound calcium (50%). As the albumin concentration affects the total plasma calcium concentration, corrected total plasma calcium values are usually reported (2.20–2.70 mmol litre^{-1}). However, only ionised (free) calcium is physiologically active (1.1–1.3 mmol litre^{-1}).[1,2,6] Most blood gas analysers can measure ionised calcium levels.

Approximately 8–10 g of unbound calcium are filtered by the glomerular apparatus daily, but more than 98% of this calcium is reabsorbed by the kidneys. The majority is reabsorbed via a PTH-independent mechanism in the proximal tubule.[1,6]

The effects of PTH and 1,25-dihydroxycholecalciferol on the regulation of ionised calcium have been outlined above. Calcitonin, the third hormone involved in calcium homeostasis, is produced by the parafollicular cells of the thyroid gland. It opposes osteoclastic bone resorption and increases urinary calcium excretion. It may play a role in bone formation in infants and it may also have bone protective effects during pregnancy and lactation. Generally, however, it plays a limited role in calcium homeostasis in humans.[3]

Hyperparathyroidism

Hyperparathyroidism occurs due to an increase in the secretion of PTH. This may be due to intrinsic pathology of the glands (primary or tertiary hyperparathyroidism) or due to extrinsic pathology affecting calcium homeostasis (secondary hyperparathyroidism).[2]

Primary hyperparathyroidism

Primary hyperparathyroidism is now considered to be a common endocrine disorder that is mostly diagnosed incidentally in patients who are asymptomatic or only mildly symptomatic.[1,2] Several decades ago, before the routine use of automated biochemical analysers, most patients presented with complications related to chronic hypercalcaemia; the classic "moans, stones and groans" presentation.[1,7] The disease is more common in woman and the elderly, therefore the peak incidence is in post-menopausal women.[2]

75–90% of all cases of primary hyperparathyroidism are caused by single parathyroid adenomas. 10–15% are caused by multiple adenomas or diffuse hyperplasia and less than 1% by parathyroid carcinomas. Parathyroid hyperplasia is also a feature of multiple endocrine neoplasia (MEN) type I and IIa.[1,2,6]

Clinical presentation

70–80% of patients are asymptomatic with the disease being diagnosed after an incidental finding of hypercalcaemia.[2] Typical biochemistry results show a total serum calcium that is elevated not more than 0.25 mmol litre^{-1}, serum phosphate in the low normal range and an elevated PTH level. Other abnormal results may include elevated markers of bone turnover, such as osteocalcin and bone-specific alkaline phosphatase. 25-hydroxycholecalciferol levels are usually low, while 1,25-dihydroxycholecalciferol levels are within the high normal range. 40% of patients have hypercalciuria.[8]

Only 20–30% of patients are symptomatic at the time of diagnosis.[2]

Renal manifestations

Nephrolithiasis is the commonest symptom. Severe, acute hypercalcaemia (corrected total serum calcium > 3.0 mmol litre^{-1}) may impair renal tubular function, causing a type of nephrogenic diabetes insipidus. Affected patients present with polyuria, dehydration and worsening hypercalcaemia.[1,2] Proximal renal tubular acidosis, aminoaciduria and glycosuria may also be present.[6]

Skeletal manifestations

A reduction in cortical bone density is common in patients with primary hyperparathyroidism and the risk of distal fractures seems to be increased.[1] Surgical parathyroidectomy may lead to an improvement in bone density.[1,8] Osteitis fibrosa cystica is now an uncommon finding.[6]

Neurologic manifestations

Cognitive dysfunction (impaired memory, confusion, delirium, fatigability) is frequently reported and psychiatric symptoms may include depression and personality changes.[1,2,6,8,9] Proximal muscle weakness is no longer a common complaint.[1]

Gastrointestinal manifestations

Constipation, anorexia and non-specific abdominal pain are often reported.[6,9] The incidence of peptic ulcer disease is increased as hypercalcaemia can stimulate gastrin secretion.[1] Acute pancreatitis is uncommon and usually associated with severe hypercalcaemia.[1,2]

Cardiovascular manifestations

There seems to be an association between primary hyperparathyroidism and hypertension,[2] however, hypertension usually persists after parathyroidectomy.[1,8] Severe hypertension in association with paroxysmal symptoms such as palpitations, anxiety, sweating and headaches warrants a search for a phaeochromocytoma and MEN type IIa.[1] Hypercalcaemia may also produce changes on electrocardiogram, such as shortening of the QT and ST intervals.[7,10]

Treatment

Surgical parathyroidectomy is the only cure for primary hyperparathyroidism[2] and most symptomatic patients will

present for elective parathyroidectomy. In asymptomatic patients, particularly those who are elderly with significant coexisting comorbid conditions, medical management and disease surveillance may be considered.[1,2,6]

Surgical management

There are two common surgical approaches: a bilateral neck exploration or a minimally invasive (focused) parathyroidectomy. The bilateral neck exploration involves the identification and examination of all four glands. This approach is more invasive but has a 95% success rate (up to 15% of patients have multiple adenomas) and does not require preoperative imaging studies. The minimally invasive approach can only be performed after preoperative localisation studies have been performed. The most commonly used imaging studies are technetium sestamibi scans, neck ultrasound, CT and MRI scans. During the minimally invasive approach, intraoperative measurement of serum PTH concentrations may be helpful. A reduction of PTH concentration by 50% within ten minutes of gland removal confirms successful removal of the diseased gland.[1,2,4,8] The minimally invasive approach therefore requires the availability of the necessary infrastructure and expertise to perform localisation studies and intraoperative PTH assays.[4] In some high-volume centres, endoscopic parathyroidectomies are being performed.[4]

Medical management

As most patients with primary hyperparathyroidism are asymptomatic, the focus of medical treatment should be increasing bone mineral density and reducing bone turnover. This can be achieved with agents that inhibit bone resorption, such as oral bisphosphonates, raloxifene (a selective oestrogen receptor modulator) and hormone replacement therapy.[1,2,8]

Cinacalcet is a calcimetric agent that increases the sensitivity of the CaSR to extracellular calcium. It therefore reduces the production and secretion of PTH.[1,2,8]

Management of severe hypercalcaemia

Occasionally, a patient with primary hyperparathyroidism may present with severe hypercalcaemia. Other causes of hypercalcaemia include malignancy, granulomatous disease, immobilisation, drugs and familial hypocalciuric hypercalcaemia.[1] Irrespective of the cause, the approach to the management of a hypercalcaemic crisis is the same: intravenous rehydration with 0.9% NaCl should commence at a rate of 75–150 ml/hour. More rapid administration of intravenous fluid may improve the saline diuresis effect but is also more likely to fluid overload elderly patients. Intravenous bisphosphonates (pamidronate 90 mg or zoledronic acid 4 mg) should be administered early on and calcitonin (4 units/kg subcutaneously) should be considered in patients that are very symptomatic. Steroids may be useful in malignancy induced hypercalcaemia.[9] The modern management of acute, severe hypercalcaemia no longer includes the use of furosemide and forced saline diuresis. Furosemide should only be used in patients who are at risk of fluid overload.[11] The introduction of bisphosphonates a few days prior to surgery should be avoided.[2] These drugs only become effective after a few days[9] and may therefore cause hypocalcaemia after surgery.[2]

Secondary hyperparathyroidism

In situations where plasma ionised calcium concentrations are chronically low, the CaSR initiates a compensatory increase in PTH secretion. Hypertrophy of the glands occurs even though there is no intrinsic gland pathology. Eventually, the ability of the parathyroid glands to mobilise enough calcium is exceeded, resulting in hypocalcaemia.[2,3,6] The commonest cause of secondary hyperparathyroidism is chronic kidney disease. Other causes include Vitamin D deficiency, malabsorption (post bariatric surgery for example), liver failure and pseudohypoparathyroidism. Analysis of corrected calcium, phosphate, PTH, 25-hydroxycholecalciferol and total alkaline phosphatase levels will assist with the diagnosis.[2]

Chronic kidney disease

When the glomerular filtration rate (GFR) drops below 90 ml/min/1.73m^2, 1.25-dihydroxycholecalciferol levels start to fall. This occurs because 1α-hydroxylase is inhibited by hyperphosphataemia, hyperuricaemia and metabolic acidosis. The hyperphosphataemia also directly stimulates PTH secretion.[2] In more advanced renal disease, renal PTH-resistance developes.[6] Biochemistry results usually show normal or low corrected calcium, high phosphate, high PTH, normal or low 25-hydroxycholecalciferol and high total alkaline phosphatase levels.[2]

The clinical presentation of renal osteodystrophy is variable and includes osteitis fibrosa cystica, osteomalacia, skeletal deformities, bone pain and various radiographic lesions.[6] Calcification of vascular and soft tissues (lung, heart and kidneys) is common and occurs as a result of deposition of calcium-phosphate crystals. Calciphylaxis (calcific uraemic arteriopathy) is an uncommon but serious complication that may cause extensive skin necrosis.[6]

Medical treatment aims to normalise calcium and phosphate levels, thereby suppressing PTH secretion. In most patients this can be achieved by dietary phosphate restriction, oral calcium and vitamin D supplementation and the administration of phosphate binding agents.[6,7]

In 5–10% of patients on chronic dialysis, medical therapy for secondary hyperparathyroidism fails. These patients may then require parathyroid removal.[6] A subtotal parathyroidectomy or total parathyroidectomy with forearm auto transplantation is usually performed.[6] The preoperative preparation should be the same as for any patient with chronic kidney disease and the attending anaesthetist must be mindful of the risks associated with chronic kidney disease.

Tertiary hyperparathyroidism

Tertiary hyperparathyroidism represents a state in which autonomous hypersecretion of PTH causes hypercalcaemia. It is most commonly seen in post renal transplantation patients who previously had secondary hyperparathyroidism. There is a delay in the hypertrophied parathyroid glands returning to normal baseline function. However, most patients have normal calcium levels within a year of renal transplantation and surgical intervention is very rarely necessary.[2,6]

Humoral hypercalcaemia of malignancy

Squamous cell tumours (lung, breast, renal, oesophagus) may secrete PTH-related protein (PTHrP). This peptide shares 13 amino acids with PTH and binds to the PTH receptor. Hypercalcaemia due to increased osteoclastic bone resorption is the usual presenting symptom.[1]

MEN type 1 and type 2a

MEN 1 is a rare autosomal dominant disorder that cause tumours of the parathyroid glands, the endocrine pancreas and the anterior pituitary gland. Patients usually present with hyperparathyroidism (multi-gland hyperplasia) before the other endocrine tumours present clinically.[6]

MEN 2a is also a rare autosomal dominant disorder in which there is an association between medullary thyroid carcinoma, phaeochromocytoma and hyperparathyroidism.[6]

Anaesthetic considerations for parathyroidectomy

Preoperative assessment and optimisation

Patients who present for parathyroidectomy are often elderly[2] and are therefore more likely to have significant comorbid conditions. These conditions need to be evaluated and optimised preoperatively.

Lind et al.[12] evaluated the preoperative risk factors in patients with primary hyperparathyroidism presenting for surgery. They identified a higher prevalence of cardiovascular, respiratory, renal and glucose control impairments in primary hyperparathyroidism patients when compared to age and sex matched controls.[12]

Patients with mild to moderate hypercalcaemia and no renal or cardiovascular dysfunction do not require any specific preoperative intervention.[7,10,13] Corrected calcium levels above 3 mmol/l should be corrected with saline infusions and bisphosphonate therapy. Patients in whom the corrected calcium level exceeds 3.5 mmol/l, are likely to be significantly volume depleted[1] and should be managed as a hypercalcaemic crisis (see above).

Anaesthetic technique

Bilateral neck explorations are usually performed under general anaesthesia with or without regional anaesthesia. The airway is usually intubated with an armoured endotracheal tube and the eyes should be adequately protected. The patient is positioned supine with a slight head up tilt. A bolster or cushion under the patient's shoulders assists with extending the patients neck and the head should be stabilised in a head ring.[7,13,14] The patient's arms are usually adducted to allow good surgical access to the neck. This may restrict accessibility to intravenous lines and long extension lines should be considered.[14] It is the author's practice to place bilateral superficial cervical plexus blocks under ultrasound guidance after the patient has been positioned.

There is no evidence that any specific general anaesthetic technique or combination of drugs improves outcomes. The surgical time varies between 1–3 hours and some basic principles should be followed: The patients are often osteoporotic and should be positioned carefully. Pressure points need to be padded. Longer cases require careful temperature and fluid management. In the presence of muscle weakness and hypercalcaemia, the response to muscle relaxants may be unpredictable and peripheral nerve stimulators should be used to appropriately titrate these drugs. Some surgeons still inject methylene blue intraoperatively. The dose should not exceed 5 mg/kg and rapid injections may interfere with pulse oximetry.[7,13,14] In order to exclude recurrent laryngeal nerve injury, many anaesthetists examine the position of the vocal cords,[7] usually during deep extubation (with the patient breathing spontaneously).

Minimally invasive parathyroidectomies can be performed under general anaesthesia or under regional anaesthesia (usually with the addition of sedation). Black et al.[15] compared the two techniques and found that there was no difference in the surgical success rate, morbidity or length of hospital stay between the two groups. However, patients who had their minimally invasive parathyroidectomy performed under regional anaesthesia with sedation, had significantly lower postoperative pain scores and a lower prevalence of nausea and vomiting.[15]

Postoperative complications

The recurrent laryngeal nerves innervate all the muscles of the larynx except for the cricothyroid muscles, which are innervated by the external laryngeal branches of the superior laryngeal nerves. Isolated, complete injury to the recurrent laryngeal nerve results in unopposed adduction (by the cricothyroid muscle) of the ipsilateral vocal cord. Unilateral recurrent laryngeal nerve injury usually presents with hoarseness. Bilateral recurrent laryngeal nerve injury is very uncommon but affected patients may develop stridor or airway obstruction. Such patients may require immediate reintubation.[6,7,14]

Hypocalcaemia due to removal of all four glands presents 6–24 hours postoperatively. The patients initially complain of perioral paraesthesia. This is followed by restlessness and neuromuscular irritability (positive Chvostek's and Trousseau's signs and stridor). Prolongation of the ST and QT intervals may be evident on electrocardiogram. If left untreated, severe tetany may develop.[6,7,14]

Surgical bleeding may lead to extensive haematoma formation in the neck.[7,14] Delayed management may be complicated by significant anatomical distortion of the airway, airway obstruction and difficult intubation. Soft tissue swelling and airway oedema may also complicate the postoperative course.[14]

Hypoparathyroidism

The commonest cause of hypoparathyroidism is surgical removal of all four parathyroid glands. Other causes include radiotherapy to the neck and congenital pseudohypoparathyroidism.[7]

The clinical presentation depends on the time it takes for the hypocalcaemia to develop. Acute hypocalcaemia presents as described above and should be managed with intravenous calcium gluconate or calcium chloride. Chronic hypocalcaemia presents with fatigue, muscle cramps and impaired mentation.[7] Hypocalcaemic patients presenting for surgery should have their corrected calcium normalised preoperatively, especially if they have cardiac pathology. Hyperventilation should be avoided intraoperatively.[7,14]

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