56 T_h e parathyroid glands

ANATOMY OF THE PARATHYROID GLANDS

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The developmental embryology and surgical anatomy of the parathyroid glands are intimately linked, and knowledge of both is essential for successful surgical treatment of parathy roid disease. The parathyroid glands, of which there are four, develop from the third and fourth pharyngeal pouches between the Sir Richard Owen , 1804–1892, English comparative anatomist and palaeontologist. First director of the Natural History Museum, London, UK, and Hunterian Professor at the Royal College of Surgeons of England. Ivar Viktor Sandström , 1852–1889, medical student, Uppsala, Sweden. Marcel Eugene Gley , 1857–1930, French pathologist. William J MacCallum , 1874–1944, Professor of Pathology , Johns Hopkins Hospital, Baltimore, MD, USA. Felix Mandl , 1892–1957, Professor of Surgery , Vienna, Austria. fifth and 12th weeks of gestation. They are typically described as ‘Portland brick’ (yellow/brown) in colour and weigh approximately 30 /uni00A0 mg. Approximately 13% of the popula - tion have abnormal parathyroid tissue, with 5% having a true supernumerary gland. The blood supply of both the superior and inferior parathyroid glands arises from the inferior thy - - roidal artery . While the location of the individual glands may vary significantly , there appears to be a degree of symmetry between opposite sides that can be helpful during surgical dis - section. T he inferior parathyroid gland and the thymus arise from the third pharyngeal pouch. As a result of the longer normal embryological descent, there is correspondingly more varia - tion in their anatomical position. How ever, in more than 50% of cases they are located at the inferior pole of the thyroid - gland, on the anterior, lateral or posterior surface. The gland itself is freely mobile within a glob ule of fat adjacent to the lower pole (Figure 56.1a). The superior parathyroid glands arise from the dorsal por - tion of the fourth pharyngeal pouch. As a result of their more limited embryological descent they are more constant in posi - tion. In more than 80% of patients, the superior parathyroid g lands are located at the posterior aspect of the thyroid lobe in an area 2 /uni00A0 cm in diameter, centred 1 /uni00A0 cm around the junction of the inferior thyroid artery and the r ecurrent laryngeal nerve in strict proximity to the cricothyroid junction (Figure 56.1b). - The parathyroid glands are closely associated with, but con - tained within, a halo of fat that is freely mobile over the thyroid capsule.

The aetiology, presentation, investigation • and management of secondary and tertiary hyperparathyroidism The aetiology and management of parathyroid • carcinoma

Undescended (above ITA) Below intersection ITA and RLN Mediastinal (b) In carotid sheath 1% Paraoesophageal and below ITA Figure 56.1 Potential locations of the inferior (a) and superior (b)

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CALCIUM AND PARATHYROID HORMONE REGULATION

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The parathyroid glands play a central role in the regulation of serum calcium levels through the production of the active 84-amino-acid peptide, parathyroid hormone (PTH). PTH is secreted in response to low serum calcium or high serum magnesium levels. It is initially cleaved in the liver, yielding an inactive C-terminal that is cleared by the kidneys. The N-terminal fragment is responsible for the biological activity of PTH on peripheral tissues. The active circulating molecule has a half-life of approximately 3–5 minutes in patients with normal renal function. PTH acts directly on the kidneys, bone and the gastro - intestinal tract to activate intracellular second messengers, including cyclic AMP and calcium. In the kidneys , PTH increases serum calcium levels by increasing resorption of calcium from the renal tubules and increasing the hydrox - ylation of 25-hydroxyvitamin D to the biologically active 1,25-dihydroxyvitamin D. Active vitamin D increases both the resorption of phosphorus in the kidneys and the absorption of calcium from the gastrointestinal tract. In bone, PTH acts on

2% 2% Intrathyroidal 3% 56% Related to lower pole of thyroid 28% In thyrothymic tract 9% Related to upper pole of thyroid 11% Around intersection 77% of ITA and RLN 1% Intrathyroidal 10% parathyroid glands. ITA, inferior thyroid artery; RLN, recurrent laryngeal nerve.

increasing the amount of calcium in the extracellular space (Figure 56.2). Calcitonin, which is synthesised by the parafollicular C cells of the thyroid gland, acts as the physiological antagonist to PTH. Calcitonin decreases serum calcium by decreasing bone turnover . CALCIUM AND PARATHYROID HORMONE REGULATION

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Calciphylaxis

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Calciphylaxis (calcific uraemic arteriolopathy) is a syndrome of disseminated calcification resulting in both vascular calci fication and skin necrosis. It accounts for approximately 4% of patients undergoing surgical intervention for secondary hyperparathyroidism. It presents with expanding painful cutaneous purpuric lesions, predominantly on the e xtremities, although they can also be seen on the lower abdomen. The underlying tissue calcification within the arteriolar and small vascular walls leads to ischaemic necrosis and the development of gangrene, which in turn leads to overwhelming sepsis and death. The majority of these patients will have an elevated calcium /uni00A0×/uni00A0 phosphate product but it is not usually associated with an extremely high PTH level. The underlying aetiology remains unclear but a number of potential factors have been postulated. A reduction in the serum levels of a calcification inhibitory protein, α - Heremans–Schmid glycoprotein, 2 and abnormalities in smooth muscle cell biology in uraemic patients may play a role in the development of the syndrome. Prognosis for these patients is extremely poor, with a mortality of up to 87%. An urgent parathyroidectomy has been shown to J F Heremans , 1927–1975, Professor of Medicine, Catholic University of Louvain, Belgium. Karl Schmid , 1920–2009, Biochemist, Boston Medical Center, Boston, MA, USA. amputation in these patients. It has also been associated with an increase in median survival. Calciphylaxis

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Diagnosis

Diagnosis

- PHPT is a biochemical diagnosis. Only when the disease has been confirmed biochemically should localisation studies be undertaken. Positive imaging does not confirm the diagnosis and negative findings cannot rule it out. PHPT is defined as an elevated total, or more specifically ionised, calcium in the presence of an inappropriately elevated or unsuppressed PTH. It is associated with a low serum - phosphate in the setting of normal creatinine and vitamin D lev els; 24-hour urinary excretion of calcium may be normal or elevated. It is important to perform a 24-hour urinary collection to rule out the presence of the rare familial hypocalciuric hypercalcaemia (FHH). Alkaline phosphatase may be elevated in patients in whom there is concomitant bone disease. This is important to recognise preoperatively as the surgeon should anticipate significant postoperative hypocalcaemia due to the development of hungry bone syndrome. Diagnosis

The classical symptoms associated with secondary hyperpara - thyroidism are seen less commonly now , with greater awareness of the disease and the resultant earlier medical intervention. However, prog ressive bone disease, especially bone pain, can occur with associated soft-tissue calcium deposits (Figure 56.9). The diagnosis of secondary hyperparathyroidism is characterised by hypocalcaemia or normocalcaemia with an elevated PTH. Patients have a high serum phosphate and a low vitamin /uni00A0 D. Traditional plain radiog raphs now rarely demonstrate the pathognomonic osteitis fibrosa cystica. How - ever, bone densitometry (DEXA scan) typically demonstrates osteopenia or osteoporosis. The diagnosis of secondary hyperparathyroidism is a bio - chemical one. In general, localisation studies are not under - taken as minimally invasiv e surgery is not indicated. However, neck ultrasonography can be performed to identify patients with nodular hyperplasia who may be refractory to medical management. Localisation studies are helpful in patients with recurrent disease in order to identify ectopic parathyroid tissue, especially in the mediastinum. In cases of recurrent disease, when there is no evidence of active disease in the neck and a previous allograft has been used to the forearm, selective venous sampling for PTH in the neck and the brachial vein on the side of the graft can be useful. This is known as the Casanova test and to prove that the recurrent disease is located in the grafted arm (graft hyperplasia) the ratio must be greater than 20:1.

Figure 56.9 Secondary hyperparathyroidism. Radiograph showing ectopic calci /f_i cation.

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Familial syndromes

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Familial hyperparathyroidism can be part of a well-recognised endocrine disorder, but it may also occur in isolation in a non-syndromic form. PHPT occurs as a central facet in multiple MEN type 1, type 4, type 2A, HPT-JT , autosomal dominant mild hyperparathyroidism and FHH. Familial isolated hyperparathyroidism Familial isolated hyperparathyroidism occurs when patients have PHPT without any other associated endocrinopathies. The underlying genetic abnormality has yet to be fully elucidated, but the syndrome has been linked to known mutations in the MEN1 gene, the HRPT2 gene as well as the calcium-sensing receptor gene. A significant proportion of patients will belong to the MEN /uni00A0 1 family , with documented recognised mutations but without expression of other endocrinopathies. Hyper parathyroidism should be treated with a formal bilateral neck exploration and management as per patients with MEN. MEN type 1-associated hyperparathyroidism MEN type 1 is a rare autosomal dominant syndrome consisting of tumours of the parathyroids, endocrine pancreas–duode num and the pituitary (the three Ps). It occurs in approximately 1 per 30 /uni00A0 000 individuals. It can also be associated with adrenal adenomas or carcinoma, foregut carcinoids and lipomas. Mutations, of which there are o ver 1000 identified in di ff erent families, occur in the MEN1 gene, which encodes the protein menin. Menin acts as a tumour suppressor. Patients typically present with young onset (20–30 years of age) of symptomatic hyperparathyroidism and over 95% of patients will have PHPT before the age of 40 years. Surgical intervention in MEN type 1 aims to obtain and maintain normocalcaemia for the longest time possible. In gen eral, it is associated with the presence of multig land parathyroid disease and as such has mandated a bilateral cervical explora tion with at least a subtotal parathyroidectomy and cervical thymectomy . A subtotal parathyroidectomy r emoves three and a half glands with half of the most normal-appearing para th yroid left in situ with a marking stitch to facilitate reoperative intervention. A total parathyroidectomy and forearm auto transplantation is an acceptable alternative. Detailed intra operative notes, including diagrams, should be kept. Despite meticulous and extensive surgery , the rates of both persistent and recurrent disease remain high in this group of patients (up to 62%) regardless of the type of surgery performed. Unfor tunately , the rates of postoperative permanent hypocalcaemia are also high, with published rates up to 47%. Max Wilms , 1867–1918, Professor of Surgery , University of Heidelberg, Germany . MEN type 4 is an autosomal dominant syndrome that comprises the same combination of tumours as MEN type 1 but is a rarer cause of hereditary PHPT . It arises as a result of an inactivating pathogenic variant in the cyclin-dependent kinase inhibitor CDKN1B gene. It should be managed in the same fashion as MEN type 1. MEN type 2A-associated hyperparathyroidism MEN type 2A consists of medullary thyroid carcinoma (MTC), unilateral or bilateral phaeochromocytomas and PHPT . PHPT occurs in approximately 20% of patients and is associated with mutations in codon 634 in the RET proto-oncogene. The majority of patients will be asymptomatic, with a mild elevation in calcium and asymmetrically enlarged parathyroid glands. It is extremely important that the presence of a phae - ochromocytoma is excluded prior to surgical intervention. Surgery is usually performed for MTC, with the parathyroid enlargement often being a coincidental

intraoperative finding (see Chapter 55). In this setting, with extensive surger y for MTC, the primary aim of treatment is to avoid hypoparathy - roidism. A conservative stance is adopted with resection of grossly enlarged glands, but with preservation of parathyroid tissue where possible and identification with a mar king stitch - in the neck. Hyperparathyroidism–jaw tumour syndrome HPT-JT is a rare cause of PHPT . It arises as a result of inactivating mutations in the HRPT2 / CDC73 gene on chromosome 1q21–q31, encoding parafibromin. It classically - presents with early-onset PHPT (mean age of 32 years), the aetiology of which can be either single- or multigland disease but is predominantly cystic in nature. It presents with severe hypercalcaemia and is associated with an increased risk of an underlying parathyroid carcinoma. Approximately 40% of patients will have the pathognomonic ossifying jaw fibromas of the maxilla or mandible. Other associated abnormalities include renal pathology (hamartomas, polycystic kidney disease and adult Wilms' tumours) and female patients may have uterine malignancies. Surgical intervention involves removal of all enlarged parathyroid glands. - Where there is concern for a parathyroid carcinoma, great care must be taken to avoid tumour spillage. Whether or not - an en bloc resection of the enlarged suspicious parathyroid and the adjacent thyroid lobectom y is required remains con - troversial. - Autosomal dominant mild - hyperparathyroidism - This is a rare autosomal dominant syndrome presenting with hypercalcaemia and hypercalciuria. It is associated with a mutation in the calcium-sensing receptor gene. It typically - presents in patients who are over 40 years of age and all patients have PHPT . Surgical intervention requires a bilateral neck exploration as it is associated with multigland disease. FHH is not a surgical disease and therefore preoperative diag nosis is imperative for the surgeon. FHH arises as a result of heterozygous mutations in the calcium-sensing receptor gene on chromosome 3. Benign FHH typically presents with hypercalcaemia in young (<10 years of age) asymptomatic patients. Patients with FHH have a normal or slightly elevated PTH level, increased serum magnesium levels and hypocalci uria. A low urinary calcium–creatinine clearance ratio is used to discriminate between FHH and mild PHPT . Patients rarely require intervention and surgical intervention is not indicated. Criteria for genetic testing In clinical practice, specific criteria can be employed to deter mine which patients are at the highest risk of hereditary PHPT . The current NHS England National Genomic Test Directory testing criteria from March 2019 for familial hyperparathy r oidism state that testing should be considered for patients with PHPT and a creatinine clearance ratio >0.02 who meet of the following criteria: 1 presenting before the age of 35 years or 2 presenting before the age of 45 years with one of: a proven multigland involvement or b hyperplasia on histology or c ossifying fibroma(s) of the maxilla or mandible d at least one first-degree relative with unexplained hyperparathyroidism. The testing criterion for FHH is a creatinine clearance ratio <0.02. Summary box 56.1 Primary hyperparathyroidism /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

Presentation is now typically asymptomatic rather than the classical 'bones, stones, abdominal groans and psychiatric overtones' The diagnosis of PHPT is a biochemical one Presence of an elevated ionised calcium with an inappropriately elevated/not suppressed PTH level con /f_i rms the diagnosis Sestamibi and focused neck ultrasonography are the /f_i rst-line radiological investigations 85% of cases are due to a single adenoma Minimally invasive parathyroidectomy is a safe and acceptable alternative to a four-gland exploration in the presence of localised disease Familial syndromes and disease that is not localised require a formal four-gland exploration and three-and-a-half-gland parathyroidectomy

Familial syndromes

Familial hyperparathyroidism can be part of a well-recognised endocrine disorder, but it may also occur in isolation in a non-syndromic form. PHPT occurs as a central facet in multiple MEN type 1, type 4, type 2A, HPT-JT , autosomal dominant mild hyperparathyroidism and FHH. Familial isolated hyperparathyroidism Familial isolated hyperparathyroidism occurs when patients have PHPT without any other associated endocrinopathies. The underlying genetic abnormality has yet to be fully elucidated, but the syndrome has been linked to known mutations in the MEN1 gene, the HRPT2 gene as well as the calcium-sensing receptor gene. A significant proportion of patients will belong to the MEN /uni00A0 1 family , with documented recognised mutations but without expression of other endocrinopathies. Hyper parathyroidism should be treated with a formal bilateral neck exploration and management as per patients with MEN. MEN type 1-associated hyperparathyroidism MEN type 1 is a rare autosomal dominant syndrome consisting of tumours of the parathyroids, endocrine pancreas–duode num and the pituitary (the three Ps). It occurs in approximately 1 per 30 /uni00A0 000 individuals. It can also be associated with adrenal adenomas or carcinoma, foregut carcinoids and lipomas. Mutations, of which there are o ver 1000 identified in di ff erent families, occur in the MEN1 gene, which encodes the protein menin. Menin acts as a tumour suppressor. Patients typically present with young onset (20–30 years of age) of symptomatic hyperparathyroidism and over 95% of patients will have PHPT before the age of 40 years. Surgical intervention in MEN type 1 aims to obtain and maintain normocalcaemia for the longest time possible. In gen eral, it is associated with the presence of multig land parathyroid disease and as such has mandated a bilateral cervical explora tion with at least a subtotal parathyroidectomy and cervical thymectomy . A subtotal parathyroidectomy r emoves three and a half glands with half of the most normal-appearing para th yroid left in situ with a marking stitch to facilitate reoperative intervention. A total parathyroidectomy and forearm auto transplantation is an acceptable alternative. Detailed intra operative notes, including diagrams, should be kept. Despite meticulous and extensive surgery , the rates of both persistent and recurrent disease remain high in this group of patients (up to 62%) regardless of the type of surgery performed. Unfor tunately , the rates of postoperative permanent hypocalcaemia are also high, with published rates up to 47%. Max Wilms , 1867–1918, Professor of Surgery , University of Heidelberg, Germany . MEN type 4 is an autosomal dominant syndrome that comprises the same combination of tumours as MEN type 1 but is a rarer cause of hereditary PHPT . It arises as a result of an inactivating pathogenic variant in the cyclin-dependent kinase inhibitor CDKN1B gene. It should be managed in the same fashion as MEN type 1. MEN type 2A-associated hyperparathyroidism MEN type 2A consists of medullary thyroid carcinoma (MTC), unilateral or bilateral phaeochromocytomas and PHPT . PHPT occurs in approximately 20% of patients and is associated with mutations in codon 634 in the RET proto-oncogene. The majority of patients will be asymptomatic, with a mild elevation in calcium and asymmetrically enlarged parathyroid glands. It is extremely important that the presence of a phae - ochromocytoma is excluded prior to surgical intervention. Surgery is usually performed for MTC, with the parathyroid enlargement often being a coincidental intraoperative finding (see Chapter 55). In this setting, with extensive surger y for MTC, the primary aim of treatment is to avoid hypoparathy - roidism. A conservative stance is adopted with resection of grossly enlarged glands, but with preservation of parathyroid tissue where possible and identification with a mar king stitch - in the neck. Hyperparathyroidism–jaw tumour syndrome HPT-JT is a rare cause of PHPT . It arises as a result of inactivating mutations in the HRPT2 / CDC73 gene on chromosome 1q21–q31, encoding parafibromin. It classically - presents with early-onset PHPT (mean age of 32 years), the aetiology of which can be either single- or multigland disease but is predominantly cystic in nature. It presents with severe hypercalcaemia and is associated with an

increased risk of an underlying parathyroid carcinoma. Approximately 40% of patients will have the pathognomonic ossifying jaw fibromas of the maxilla or mandible. Other associated abnormalities include renal pathology (hamartomas, polycystic kidney disease and adult Wilms' tumours) and female patients may have uterine malignancies. Surgical intervention involves removal of all enlarged parathyroid glands. - Where there is concern for a parathyroid carcinoma, great care must be taken to avoid tumour spillage. Whether or not - an en bloc resection of the enlarged suspicious parathyroid and the adjacent thyroid lobectom y is required remains con - troversial. - Autosomal dominant mild - hyperparathyroidism - This is a rare autosomal dominant syndrome presenting with hypercalcaemia and hypercalciuria. It is associated with a mutation in the calcium-sensing receptor gene. It typically - presents in patients who are over 40 years of age and all patients have PHPT . Surgical intervention requires a bilateral neck exploration as it is associated with multigland disease. FHH is not a surgical disease and therefore preoperative diag nosis is imperative for the surgeon. FHH arises as a result of heterozygous mutations in the calcium-sensing receptor gene on chromosome 3. Benign FHH typically presents with hypercalcaemia in young (<10 years of age) asymptomatic patients. Patients with FHH have a normal or slightly elevated PTH level, increased serum magnesium levels and hypocalci uria. A low urinary calcium–creatinine clearance ratio is used to discriminate between FHH and mild PHPT . Patients rarely require intervention and surgical intervention is not indicated. Criteria for genetic testing In clinical practice, specific criteria can be employed to deter mine which patients are at the highest risk of hereditary PHPT . The current NHS England National Genomic Test Directory testing criteria from March 2019 for familial hyperparathy r oidism state that testing should be considered for patients with PHPT and a creatinine clearance ratio >0.02 who meet of the following criteria: 1 presenting before the age of 35 years or 2 presenting before the age of 45 years with one of: a proven multigland involvement or b hyperplasia on histology or c ossifying fibroma(s) of the maxilla or mandible d at least one first-degree relative with unexplained hyperparathyroidism. The testing criterion for FHH is a creatinine clearance ratio <0.02. Summary box 56.1 Primary hyperparathyroidism /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

Presentation is now typically asymptomatic rather than the classical 'bones, stones, abdominal groans and psychiatric overtones' The diagnosis of PHPT is a biochemical one Presence of an elevated ionised calcium with an inappropriately elevated/not suppressed PTH level con /f_i rms the diagnosis Sestamibi and focused neck ultrasonography are the /f_i rst-line radiological investigations 85% of cases are due to a single adenoma Minimally invasive parathyroidectomy is a safe and acceptable alternative to a four-gland exploration in the presence of localised disease Familial syndromes and disease that is not localised require a formal four-gland exploration and three-and-a-half-gland parathyroidectomy

Hypercalcaemic crisis presentation and management

Hypercalcaemic crisis: presentation and management

Hypercalcaemia is documented in 0.5% of the general population and in up to 5% of hospitalised patients. The vast majority are asymptomatic with a mild to moderate elevation of serum calcium (<3 /uni00A0 mmol/L and 3–3.5 /uni00A0 mmol/L, respec tively) and respond to treatment of the underlying aetiology with associated dietary modification. A small proportion of patients will present symptomatically with a total calcium of >3.5 /uni00A0 mmol/L. This is referred to as a hypercalcaemic crisis and requires ag gressive medical management. Although symptoms can be varied, the typical presentation is of acute confusion, abdominal pain, vomiting, dehydration and anuria. Prolongation of the PR interval with a shortened QT interval can be identified on an electrocardiog ram (ECG) prior to potentially lethal cardiac arrhythmias. Where the cal cium is >4.5 /uni00A0 mmol/L, coma and cardiac arrest can occur. Treatment revolves around increasing renal excretion of calcium, reducing skeletal release of calcium and treatment of the underlying cause. Aggressive rehy dration plays a pivotal role. Typically , 200–500 /uni00A0 mL/h of normal saline is given to maintain a urine output >100 /uni00A0 mL/h, with the caveat that this may be modified to account for associated patient comorbidi ties. Once intravascular volume has been adequately restored, loop diuretics, such as furosemide, can be used to enhance the renal excretion of calcium. The majority of patients will have normalisa tion of their calcium with these simple measures. In patients with advanced malignancy and a serum calcium level >3 /uni00A0 mmol/L, agents that blunt the release of calcium from skeletal stores may be required. First-line treatment includes administration of bisphosphonates. These are pyrophosphate analogues that inhibit osteoclast activity in areas of high bone turnover. In the acute setting, these are given intravenously owing to poor absorption in the gastrointestinal tract. Calci tonin can be used to both decrease osteoclastic activity and increase renal excretion of calcium. It has a short duration of action and is usually used as a bridge to reduce calcium until the sustained action of the bisphosphonates is seen. Finally , glucocorticoids (prednisolone) can be used to enhance the action of calcitonin. T hey increase calciuresis and decrease intestinal absorption of calcium. As a result, they may also play a role in diseases associated with vitamin D excess. Hypercalcaemic crisis: presentation and management

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Introduction

INTRODUCTION

The parathyroid glands were first described by Sir Richard Owen in a neck dissection of an Indian rhinoceros at the London Zoological Gardens in 1850. Credit for recognition of the ‘glandulae parathyreoidae’ goes, however, to Sandström, who published a monograph in 1887 on dissection of the para thyroid glands and their blood supply in animals and human cadavers. Unfortunately , Sandström committed suicide at the age of 37 and it was not until the 1890s that his work was rediscover ed by Gley , who associated tetany following thyroid surgery with removal of the parathyroid glands. In 1905, MacCallum found that he could relieve postoperative tetany by the injection of parathyroid extract. While the association between parathyroid enlargement and bone disease was reported in 1907, it was not until 1925 that the first parathyroid ectomy was performed by Mandl in Vienna on Albert Gahne, a tram conductor with severe primary hyperparathyroidism (PHPT) and osteitis fibrosa cystica.

Learning objectives

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To understand: The anatomy of the parathyroid glands • The physiology of calcium regulation • The underlying causes of hypercalcaemia and appropriate • emergency management The aetiology, presentation, investigation and • management of primary hyperparathyroidism and associated special cases Learning objectives

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Localisation studies

Localisation studies

- Historically , preoperative localisation studies for PHPT were considered less important than identifying an experienced surgeon. However, with a shift away from the traditional four- gland (cervical neck) exploration to more minimally invasive procedures, accurate preoperative identification is critically important to guide surgical strategy . There are a variety of both non-invasive and invasive studies commonly in use. Non-invasive radiology includes nuclear medicine-based studies, ultrasonography and four- dimensional (4D) computed tomography (CT) scanning. Invasiv e imaging is largely reserved for reoperative surgery and includes ultrasound or CT-guided fine-needle aspiration with

In my opinion, the only localising study required in a patient with untreated primary hyperparathyroidism is to localise an experienced parathyroid surgeon. John Doppman, 1986

venous sampling for the PTH gradient. Nuclear medicine-based studies (sestamibi scanning) The use of sestamibi (2-methoxy-2-methylpropylisonitrile [MIBI]) for parathyroid localisation was first described in 1989 and is now regarded as the most accurate and reliable method for imaging the parathyroid glands. It is safe and reproducible and, while it has a sensitivity and specificity similar to ultra sonography , it may image glands in ectopic positions better (Figure 56.3a). Sestamibi accumulates in mitochondria and therefore washes out at di ff erential rates depending on the number of mitochondria within individual tissues. Para thyroid adenomas often have a high concentration of oxyphilic cells with high mitochondrial content. T hese retain tracer, and adenomas are therefore associated with a slow washout when compared with the thyroid gland. There are three di ff erent protocols for ses tamibi scanning: single-isotope dual-phase scan, dual-isotope Karl Hürthle , 1866–1945, histopathologist, Breslau, Germany (now Wroc ł aw , Poland). tomography (SPECT). The sensitivity and specificity of ses - tamibi, regardless of the protocol used, are 79% and 90%, respectively . False positives are rare but may arise from some solid thyroid nodules, such as Hürthle cell nodules, that are associa ted with high oxyphilic content. These can be reduced by the addition of a thyroid-specific radioactive tracer, such as 99 Tc-pertechnetate and subsequent subtraction images. Ultrasonography - Ultrasonography is a non-invasive, inexpensive method of imaging the parathyroid glands (Figure 56.3b). Parathyroid adenomas are typically oval or elongated, bi- or multilobed hypoechoic structures. Rarely , adenomas may be cystic or heterogeneous in nature. Giant adenomas are described as those over 3 /uni00A0 cm in size. Ultrasonography is not associated with any radiation exposure and has the advantage of being able to identify and facilitate biopsy of any concomitant thyroid - pathology . However, ultrasonography is operator, lesion size and location dependent. Critically , ultrasonography may

(a) Figure 56.3 Sestamibi scan (a) demonstrating right inferior adenoma, with concordant ultrasonography (b) . (b)

or retrotracheal areas. It can also be di ffi cult to di ff erentiate between a small parathyroid gland and a normal-appearing lymph node. A meta-analysis of preoperative localisation techniques in PHPT demonstrated that ultrasonography and sestamibi-SPECT have comparable accuracy , with pooled sensitivities of 76.1% and 78.9%, respectively , and positive predictive values (PPVs) of 93.2% and 90.7%, respectively (Krakauer et al ., 2016). Four-dimensional computed tomography scanning/positron emission tomography– computed tomography Multiphase CT imaging (4D-CT) has become widely utilised to localise disease (Figure 56.4). It gives both anatomical and functional information about the parathyroid glands. Using precontrast, postcontrast and delayed images, it demonstrates not only detailed anatomical localisation but, combined with rapid uptake and washout, allows hyperfunctioning glands to be di ff erentiated from lymph nodes that demonstrate a progressive enhancement pattern. The potential disadvantage of 4D-CT scanning is the higher radiation dose when compared with traditional imaging modalities. Modification of the protocol now allows fewer phases to be obtained without compromising outcomes. The initial study in 2006 reported a sensitivity of 88% for lateralisation and 70% for localisation of parathyroid adenomas (Rodgers et al ., 2006). A more recent meta-analysis, although limited by the small number of studies, demonstrated a sensitivity and PPV of 89.4% and 93.5%, respectively , when 4D-CT was used as the primary imaging modality . This was reduced to 71.8% and 74.9%, respectively , in cases of negative or inconclusive prior imaging (Cheung et al ., 2012). Positron emission tomography (PET) scanning remains expensive and is not widely available. However, recent data 18 suggest that there may be an incr emental value to F-fluoro choline PET with the addition of CT scanning for localisation of ectopic adenomas. Magnetic resonance imaging Magnetic resonance imaging (MRI) is not commonly used to image the parathyroid glands. However, on T2-weighted images, enlarged parathyroid glands demonstrate significantly increased intensity . In reoperative cases or where the adenoma is located in the mediastinum, MRI may be beneficial, with higher reported sensitivities (50–88%). While the sensitivity of MRI is slightly better than that for CT (64–88%) in primary disease, it has significant limitations. It is expensive, patients can be poorly compliant owing to claustrophobia and the resolution for normal glands or adenomas <5 /uni00A0 mm is poor. Similarly , it can be di ffi cult to localise superior glands because of their posterior location, which allows them to be obscured by the thyroid gland. Parathyroid angiography and venous sampling for parathyroid hormone Parathyroid angiography is reserved for reoperative cases and is now rarely required owing to improvements in non-invasive imaging modalities. It involves examination of - both thyrocervical trunks, both internal mammary arteries and both carotids, with occasional selective superior thyroid artery catheterisation. Vascular parathyroid adenomas appear as a persistent oval or round ‘stain’ on angiography . Serious complications such as contrast-induced renal failure, embolisation and neurological damage have limited its utility . Selective venous sampling for PTH can allow accurate localisation of adenomas but an experienced interventional radiologist is vital for success. The venous drainage of the lesion is established when there is a twofold drop in the PTH betw een the sampled blood and the serum PTH. The sensitiv - ity is reported to be 80% and is equally e ff ective in localising cervical and mediastinal adenomas. However, the false-positive to reoperative rate of between 6% and 18% limits its utility cases.

(b) Figure 56.4 (a, b) Four-dimensional computed tomography scanning demonstrating a right inferior parathyroid adenoma (arrows).

Surgical management The mainstay of treatment for PHPT is surgery , addressing the underlying aetiology and allowing not only resolution of biochemical abnormalities but also sustained improvements in end-organ damage. Traditionally a bilateral cervical explora tion was performed with reported cure rates of 95–98%. With improvements in preoperative radiological localisation, a more minimally invasive approach has been developed and widely adopted (Figure 56.5). All symptomatic patients should be o ff ered surgery . An expert panel published recommendations on which asymp tomatic patients should be considered for surgical intervention (Table 56.2). Guidelines from the American Association of Endocrine Surgeons have more liberal indications for surgery . These included patients with cognitive or psy chiatric symp toms attributable to PHPT , cardiovascular disease (excluding hypertension) and more non-specific symptoms, such as muscle weakness, impaired functional capacity and abnormal sleep patter ns. When criteria have been met and where a single ade noma has been confidently identified by radiological means, a /uni25CF /uni25CF /uni25CF /uni25CF versely , where there is discordant imaging or where imaging fails to identify any parathyroid abnormalities, then a bilateral neck exploration and a three-and-a-half-gland parathyroidec - tomy or a four -gland parathyroidectomy and autotransplanta - tion should be performed. Consent for a parathyroidectomy must include the - possibility of recurrent laryngeal nerve damage (risk <1%), permanent hypoparathyroidism (requiring lifelong calcium and vitamin D supplementation; risk 0.5%) and persistent (5%) or recurrent hyperparathyroidism. Persistent disease is defined as an elevated serum calcium within 6 weeks of surgical intervention and recurrent disease is defined as an increase in - calcium levels after 6 months but with an intervening period of normocalcaemia. Minimally invasive (focused) parathyroidectomy - Minimally invasive approaches are based on the principle that over 80% of individuals with PHPT have a single adenoma. Although there is no strict definition of the procedure, it commonly refers to the removal of a localised abnormal - parathyroid gland through an incision less than 3 /uni00A0 cm in length (Figure 56.6). The term encompasses open approaches (central and lateral incisions) and video-assisted and radio- guided parathyroidectomies. A number of randomised studies have shown that the focused approach has similar cure rates to

TABLE 56.2 Consensus guidelines for surgical intervention in asymptomatic primary hyperparathyroidism. Measurement of 0.25 /uni00A0 mmol/L (1.0 /uni00A0 mg/dL)

above the upper limit serum calcium of normal Skeletal BMD by DEXA; T score –2.5 at lumbar spine, total hip, femoral neck or distal one- third of radius Vertebral fracture Renal Creatinine clearance <60 /uni00A0 mL/min 24-hour urinary calcium >10 /uni00A0 mmol/dL (>400 /uni00A0 mL/day) or increased risk of stone formation by risk analysis Age <50 years BMD, bone mineral density; DEXA, bone densitometry. Adapted from Bilezikian et al . (2014). Concordant Discordant MIBI and US imaging imaging Pre-op

marking 4D CT with US Pre-op 4 gland MIP marking with exploration US and MIP Figure 56.5 Localisation paradigm and management strategies. 4D /uni00A0 CT, four-dimensional computed tomography; MIBI, 2-methoxy-2 methylpropylisonitrile; MIP , minimally invasive parathyroidectomy; US, ultrasonography. (a) (b)

Figure 56.6 (a) Minimally invasive parathyroidectomy through a lateral approach; (b) the excised parathyroid adenoma.

hypocalcaemia, shorter operating times, potentially less pain and better cosmesis. The need to convert from a focused to a cervical explora tion may be guided by the use of intraoperative PTH mea surements. Routine use is, however, controversial owing to high false-positive and false-negative rates. The basic concept is that the half-life of circulating PTH is 3–5 minutes and there should therefore be a significant dr op detected in the plasma PTH following resection of a single adenoma. If no such drop is detected, then multigland disease may be sus pected and conversion to a bilateral neck exploration should be considered. The Miami criteria were developed to determine the extent of resection. A drop in the PTH into the normal range and to less than half the maximum preoperative PTH at 10 /uni00A0 minutes appears to accurately predict single-gland disease (Figure 56.7). Bilateral neck exploration A traditional cervical neck exploration is required where imaging is negative or discordant, in MEN (type 1 or type 2A) or in lithium-induced PHPT . A

transverse collar (Kocher’s) incision is made and the subplatysmal plane developed. The deep cervical fascia is divided between the strap muscles and these are retracted. The thyroid lobes are mobilised and the middle thyroid vein may be divided when present. Identification of the recurrent laryngeal nerve and the middle thyroid artery allows a starting point for a systematic exploration (see Chapter 55). All four glands are identified. Three and a half glands ar e resected, with half of a vascularised parathyroid left in situ . The other half of the gland should be sent for frozen section to confirm the presence of parathyroid tissue (Figure 56.8). Ideally the most normal-appearing parathyroid is left in situ . With this caveat in mind, where possible an inferior gland should be left. It is marked with a non-absorbable suture to aid identification in the presence of recurrent disease, where resection can be achieved without increasing the risk of damage to the recurrent laryngeal nerve. Alternatively , all four glands can be resected and a forearm autotransplant created. Small pieces of parathyroid are sutured into pockets created in the brachioradialis muscle. Cure rates and rates of persistent and recurrent disease appear to be similar, regardless of the Emil Theodor Kocher , 1841–1917, surgeon, Berne, Switzerland, awarded the Nobel Prize in Physiology or Medicine in 1909 for his research on the thyroid. - - - type of procedure used. However, in recurrent disease it can be di ffi cult to identify the location of the recurrent tissue when an autotransplant is performed. Thymectomy and resection of mediastinal adenomas The incidence of clinically significant supernumerary glands is increased in patients with multigland disease or those with hereditary syndromes. A thymectomy should be routinely undertaken for patients with MEN1 - associated PHPT or in secondary hyperparathyroidism. A cervical thymectomy is performed by dissecting close to the thymic capsule, exploring the cervical part of the gland. The mediastinal part of the gland can be removed by gentle upwards traction, with ligation of the veins draining into the innominate vein. The end of the

120 100 80 60 40 20 % PTH remaining 0 0 5 10 15 Time (min) Figure 56.7 Miami criteria for intraoperative parathyroid hormone (PTH) measurement. Drop of PTH into the normal range and less than half the maximum value at 10 minutes postresection. (b) Figure 56.8 Parathyroidectomy with exposure of the left superior and inferior parathyroid glands (white arrows) in situ (a) and left superior gland mobilised on its vascular pedicle (b) .

sternotomy is not required where a prophylactic thymectomy is being performed. Mediastinal adenomas are rare, accounting for less than 1% of all parathyroid adenomas. They will be typically identi fied on preoperative imaging. Resection can be achieved either b y an open sternotomy or increasingly by a thoracoscopic approach. A minimally invasive approach can be particularly e ff ective where the abnormal gland lies immediately deep to the mediastinal pleura. It can confer significant advantages in length of hospital stay and complication rates. Localisation studies

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respectively , in cases of negative or inconclusive prior imaging (Cheung et al ., 2012). Positron emission tomography (PET) scanning remains expensive and is not widely available. However, recent data 18 suggest that there may be an incr emental value to F-fluoro choline PET with the addition of CT scanning for localisation of ectopic adenomas. Magnetic resonance imaging Magnetic resonance imaging (MRI) is not commonly used to image the parathyroid glands. However, on T2-weighted images, enlarged parathyroid glands demonstrate significantly increased intensity . In reoperative cases or where the adenoma is located in the mediastinum, MRI may be beneficial, with higher reported sensitivities (50–88%). While the sensitivity of MRI is slightly better than that for CT (64–88%) in primary disease, it has significant limitations. It is expensive, patients can be poorly compliant owing to claustrophobia and the resolution for normal glands or adenomas <5 /uni00A0 mm is poor. Similarly , it can be di ffi cult to localise superior glands because of their posterior location, which allows them to be obscured by the thyroid gland. Parathyroid angiography and venous sampling for parathyroid hormone Parathyroid angiography is reserved for reoperative cases and is now rarely required owing to improvements in non-invasive imaging modalities. It involves examination of - both thyrocervical trunks, both internal mammary arteries and both carotids, with occasional selective superior thyroid artery catheterisation. Vascular parathyroid adenomas appear as a persistent oval or round ‘stain’ on angiography . Serious complications such as contrast-induced renal failure, embolisation and neurological damage have limited its utility . Selective venous sampling for PTH can allow accurate localisation of adenomas but an experienced interventional radiologist is vital for success. The venous drainage of the lesion is established when there is a twofold drop in the PTH betw een the sampled blood and the serum PTH. The sensitiv - ity is reported to be 80% and is equally e ff ective in localising cervical and mediastinal adenomas. However, the false-positive to reoperative rate of between 6% and 18% limits its utility cases.

(b) Figure 56.4 (a, b) Four-dimensional computed tomography scanning demonstrating a right inferior parathyroid adenoma (arrows).

Surgical management The mainstay of treatment for PHPT is surgery , addressing the underlying aetiology and allowing not only resolution of biochemical abnormalities but also sustained improvements in end-organ damage. Traditionally a bilateral cervical explora tion was performed with reported cure rates of 95–98%. With improvements in preoperative radiological localisation, a more minimally invasive approach has been developed and widely adopted (Figure 56.5). All symptomatic patients should be o ff ered surgery . An expert panel published recommendations on which asymp tomatic patients should be considered for surgical intervention (Table 56.2). Guidelines from the American Association of Endocrine Surgeons have more liberal indications for surgery . These included patients with cognitive or psy chiatric symp toms attributable to PHPT , cardiovascular disease (excluding hypertension) and more non-specific symptoms, such as muscle weakness, impaired functional capacity and abnormal sleep patter ns. When criteria have been met and where a single ade noma has been confidently identified by radiological means, a /uni25CF /uni25CF /uni25CF /uni25CF versely , where there is discordant imaging or where imaging fails to identify any parathyroid abnormalities, then a bilateral neck exploration and a three-and-a-half-gland parathyroidec - tomy or a four -gland parathyroidectomy and autotransplanta - tion should be performed. Consent for a parathyroidectomy must include the - possibility of recurrent laryngeal nerve damage (risk <1%), permanent hypoparathyroidism (requiring lifelong calcium and vitamin D supplementation; risk 0.5%) and persistent (5%) or recurrent hyperparathyroidism. Persistent

disease is defined as an elevated serum calcium within 6 weeks of surgical intervention and recurrent disease is defined as an increase in - calcium levels after 6 months but with an intervening period of normocalcaemia. Minimally invasive (focused) parathyroidectomy - Minimally invasive approaches are based on the principle that over 80% of individuals with PHPT have a single adenoma. Although there is no strict definition of the procedure, it commonly refers to the removal of a localised abnormal - parathyroid gland through an incision less than 3 /uni00A0 cm in length (Figure 56.6). The term encompasses open approaches (central and lateral incisions) and video-assisted and radio- guided parathyroidectomies. A number of randomised studies have shown that the focused approach has similar cure rates to

TABLE 56.2 Consensus guidelines for surgical intervention in asymptomatic primary hyperparathyroidism. Measurement of 0.25 /uni00A0 mmol/L (1.0 /uni00A0 mg/dL) above the upper limit serum calcium of normal Skeletal BMD by DEXA; T score –2.5 at lumbar spine, total hip, femoral neck or distal one- third of radius Vertebral fracture Renal Creatinine

clearance <60 /uni00A0 mL/min 24-hour urinary calcium >10 /uni00A0 mmol/dL (>400 /uni00A0 mL/day) or increased risk of stone formation by risk analysis Age <50 years BMD, bone mineral density; DEXA, bone densitometry. Adapted from Bilezikian et al . (2014). Concordant Discordant MIBI and US imaging imaging Pre-op marking 4D CT with US Pre-op 4 gland MIP marking with exploration US and MIP Figure 56.5 Localisation paradigm and management strategies. 4D /uni00A0 CT, four-dimensional

computed tomography; MIBI, 2-methoxy-2 methylpropylisonitrile; MIP , minimally invasive parathyroidectomy; US, ultrasonography. (a) (b)

Figure 56.6 (a) Minimally invasive parathyroidectomy through a lateral approach; (b) the excised parathyroid adenoma.

hypocalcaemia, shorter operating times, potentially less pain and better cosmesis. The need to convert from a focused to a cervical explora tion may be guided by the use of intraoperative PTH mea surements. Routine use is, however, controversial owing to high false-positive and false-negative rates. The basic concept is that the half-life of circulating PTH is 3–5 minutes and there should therefore be a significant dr op detected in the plasma PTH following resection of a single adenoma. If no such drop is detected, then multigland disease may be sus pected and conversion to a bilateral neck exploration should be considered. The Miami criteria were developed to determine the extent of resection. A drop in the PTH into the normal range and to less than half the maximum preoperative PTH at 10 /uni00A0 minutes appears to accurately predict single-gland disease (Figure 56.7). Bilateral neck exploration A traditional cervical neck exploration is required where imaging is negative or discordant, in MEN (type 1 or type 2A) or in lithium-induced PHPT . A transverse collar (Kocher’s) incision is made and the subplatysmal plane developed. The deep cervical fascia is divided between the strap muscles and these are retracted. The thyroid lobes are mobilised and the middle thyroid vein may be divided when present. Identification of the recurrent laryngeal nerve and the middle thyroid artery allows a starting point for a systematic exploration (see Chapter 55). All four glands are identified. Three and a half glands ar e resected, with half of a vascularised parathyroid left in situ . The other half of the gland should be sent for frozen section to confirm the presence of parathyroid tissue (Figure 56.8). Ideally the most normal-appearing parathyroid is left in situ . With this caveat in mind, where possible an inferior gland should be left. It is marked with a non-absorbable suture to aid identification in the presence of recurrent disease, where resection can be achieved without increasing the risk of damage to the recurrent laryngeal nerve. Alternatively , all four glands can be resected and a forearm autotransplant created. Small pieces of parathyroid are sutured into pockets created in the brachioradialis muscle. Cure rates and rates of persistent and recurrent disease appear to be similar, regardless of the Emil Theodor Kocher , 1841–1917, surgeon, Berne, Switzerland, awarded the Nobel Prize in Physiology or Medicine in 1909 for his research on the thyroid. - - - type of procedure used. However, in recurrent disease it can be di ffi cult to identify the location of the recurrent tissue when an autotransplant is performed. Thymectomy and resection of mediastinal adenomas The incidence of clinically

significant supernumerary glands is increased in patients with multigland disease or those with hereditary syndromes. A thymectomy should be routinely undertaken for patients with MEN1 - associated PHPT or in secondary hyperparathyroidism. A cervical thymectomy is performed by dissecting close to the thymic capsule, exploring the cervical part of the gland. The mediastinal part of the gland can be removed by gentle upwards traction, with ligation of the veins draining into the innominate vein. The end of the

120 100 80 60 40 20 % PTH remaining 0 0 5 10 15 Time (min) Figure 56.7 Miami criteria for intraoperative parathyroid hormone (PTH) measurement. Drop of PTH into the normal range and less than half the maximum value at 10 minutes postresection. (b) Figure 56.8 Parathyroidectomy with exposure of the left superior and inferior parathyroid glands (white arrows) in situ (a) and left superior gland mobilised on its vascular pedicle (b) .

sternotomy is not required where a prophylactic thymectomy is being performed. Mediastinal adenomas are rare, accounting for less than 1% of all parathyroid adenomas. They will be typically identi fied on preoperative imaging. Resection can be achieved either b y an open sternotomy or increasingly by a thoracoscopic approach. A minimally invasive approach can be particularly e ff ective where the abnormal gland lies immediately deep to the mediastinal pleura. It can confer significant advantages in length of hospital stay and complication rates.

Management

Management

Renal transplantation remains the only definite treatment for secondary hyperparathyroidism. Other therapies are a bridge to this or aim to provide symptom relief. Standard manage - ment includes replacement of calcium and vitamin D and the reduction of phosphate levels by the use of phosphate binders. Treatment of this disease changed radically with the introduc - tion of calcimimetic drugs, such as cinacalcet. Calcimimetics alter the set point of the calcium-sensing receptor, thereby reducing the constant stimulation of the parathyroid glands and lowering the PTH lev el. This obviously does not address the underlying renal disease. It remains controversial as to which patients may benefit from the use of calcimimetics and which patients may benefit from earlier surgical intervention. Indications for pursuing medical management include those patients who are deemed non-surgical candidates by reason of medical comorbidities. Similarly , where there is persistent or recurrent disease, the origin of which cannot be clearly elucidated, surgical management should be avoided. However, there are definite indications for surgical intervention in secondary hyperparathyroidism (Table 56.3), although these have been modified to reflect the current use, where available, of calcimimetics (Table 56.4). There are a wide variety of operations that can be uti - lised for the management of secondary hyperparathyroidism, none of which appears significantly superior in terms of clin - ical outcomes (persistent or recurrent disease). These include a subtotal parathyroidectomy , a total para thyroidectomy with autograft or a total parathyroidectomy without autograft. Cryopr eservation of resected tissue, where available, should be - /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

TABLE 56.3 Indications for surgical intervention in secondary hyperparathyroidism. Essential components 1. Persistently high serum level of intact PTH >500 /uni00A0 pg/mL 2. Hyperphosphataemia (serum PO

> 6 /uni00A0 mg/dL) or hypercalcaemia 4 (serum Ca >2.5 /uni00A0 mmol/L or 10 /uni00A0 mg/dL) which is refractory to medical management 3

3.

Estimated volume of the largest gland >300–500 /uni00A0 mm or long axis >1 /uni00A0 cm Clinical /f_i ndings If patients have one of these symptoms, parathyroidectomy should be recommended: Severe osteitis /f_i brosa with associated high bone turnover Subjective symptoms (bone and joint pain, arthralgia, muscle weakness, irritability, pruritus, depression) Progressive ectopic calci /f_i cation Calciphylaxis Progressive reduction in bone mineral content Anaemia resistant to ESA Dilated cardiomyopathy/cardiac failure ESA, erythropoietin-stimulating agent; PTH, parathyroid hormone.

/uni25CF /uni25CF /uni25CF /uni25CF performed in cases of significant postoperative hypocalcaemia. The first two procedures are most widely accepted and the type of operation performed depends upon the surgeon. A subtotal parathyroidectomy is where three and a half parathyroid glands are excised, with the remnant being marked with a non-absorbable stitch to facilitate identification in the event of recur rent disease. A biopsy of the final gland that is to be left in situ is mandatory to confirm the presence of residual parathyroid tissue. Ideally an inferior gland is left in situ to facil itate reoperative surgery and minimise potential damage to the recurrent laryngeal nerve in that setting (Figure 56.10). A total parathyroidectomy with a forearm autograft in volves removal of all parathyroid tissue in the neck, with reimplantation of a small amount of morcellated tissue within a pocket formed in the brachioradialis muscle. Overall, regardless of the operative approach utilised the cure rate ranges between 90% and 96%, with similar complication rates. A randomised study looking at 40 patients who underwent either a subtotal or total parathy roidectomy with autotransplant demonstrated no significant di ff erence between the two operations in terms of e ffi cacy and recurrence rate (Rothm und et al ., 1991). The response to surgical intervention is often dramatic. The biochemical parameters may resolve almost immediately and appear to be sustained for up to 3 years postoperatively . Patients subjectively report improvements in the symptoms of secondary hyperparathyroidism, including bone pain, pruritus, fatigue and depression. Finally , bone metabolism is improved with an approximate 10% increase in trabecular bone, with almost immediate suppression of bone resorption and acceleration of new bone formation. Secondary hyperparathyroidism /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

management of secondary hyperparathyroidism (SHPT) in the era of calcimimetics. When SHPT is refractory to vitamin D replacement or vitamin D analogues and prolonged survival is anticipated Severely impaired quality of life owing to either SHPT or intolerance to calcimimetics When suf /f_i cient reduction in parathyroid hormone cannot be achieved with use of calcimimetics Thyroid surgery is also required (thyroid carcinoma) Figure 56.10 Subtotal parathyroidectomy for parathyroid hyperplasia. Right inferior gland biopsied and half left in situ . Primarily due to underlying chronic kidney disease Associated with parathyroid hyperplasia Diagnosis is made biochemically with a low or normal calcium and an elevated PTH. High phosphate levels and low vitamin D levels are seen No localisation studies are required Mainstay of treatment is renal transplantation. Medical management with calcium and vitamin D replacements and phosphate binders is a bridge to transplantation Use of calcimimetics has reduced the requirement for surgical intervention Subtotal parathyroidectomy remains the surgical intervention of choice when indicated

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PARATHYROID CARCINOMA

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Parathyroid carcinoma is a rare malignancy occurring in approximately 1% of cases of PHPT , with an estimated prevalence of 0.005% of all cancers. While the aetiology remains unclear, recent advances in molecular biology suggest that there may be an underlying genetic basis. Currently , a history of previous neck irradiation remains the only known environmental risk factor. However, given that it can arise in patients with end-stage renal disease as well as in those with MEN type 1, malignant transformation in hyperplastic glands may also occur. A significant proportion of patients (>10%) with a para thyroid carcinoma will have HPT-JT . The underlying mutation is in the HRPT2 / CDC73 gene at chromosome 1q21–q31, a tumour suppressor gene that encodes the protein parafibromin. Parafibromin is involved in the regulation of cellular transcrip tion and histone modification. HRPT2 mutations, leading to inactivation of parafibromin, are therefore an important con tributor to the pathogenesis of parathyroid carcinoma. Simi larly , up to 18% of patients with a parathyroid carcinoma will have an inactivating mutation of the PRUNE2 gene, located on chromosome 9q21.2. This is a tumour suppressor gene that encodes the RAS homologue family member A, leading to sup pression of oncogenic cellular transformation. Parathyroid carcinoma remains di ffi cult to diagnose preoperatively as it biochemically resembles PHPT . There are, however, a number of suggestive features. First, the diagnosis is typically made a decade earlier, with an equal gender preponderance when compared with PHPT . Second, a greater proportion of these patients will be symptomatic at presentation. A palpable neck mass is found in 36–52% of patients with parathyroid carcinomas but rarely (<5%) in cases of PHPT . Finally , the biochemical abnormalities tend to be 3.97 /uni00A0 mmol/L and a PTH level 5–10 times the normal range. The leading cause of morbidity and mortality from para - thyroid carcinoma is hypercalcaemia due to inappropriate PTH secretion. Tr eatment is focused on controlling hypercal - caemia and removal of the carcinoma where possible . Surgery remains the mainstay of treatment for primary presentations and locally recurrent disease. Complete resection of the tumour, av oiding spillage, is vital in preventing seeding and thus recurrent disease. En bloc resection of the tumour, asso - ciated thyroid lobectomy and central neck dissection remain controversial. Complete R0 resection was thought to provide the only means of a cure. However, a number of r ecent studies have failed to demonstrate an improvement in local r ecurrence rates with such comprehensive resection. Adjuvant chemotherapy has not been shown to confer a disease-free or overall survival benefit. Use of external beam radiotherapy should be con - sidered on an individual basis. Traditionally , it has not been deemed e ff ective, but more recent single-institution case series challenge this assumption. It may be considered where it is di ffi cult to achieve a complete surgical resection or in patients with m ultifocal recurrent soft-tissue deposits. Histological confirmation of a parathyroid carcinoma remains di ffi cult. The World Health Organization criteria (2017) for the diagnosis of a parathyroid carcinoma emphasise the need for definite invasion of the sur rounding soft tissue and/or metastatic disease. The classical description that included trabecular architecture, mitotic figures, thick fibrous bands and capsular and vascular invasion is largely non-specific. New molecular markers may aid the diagnosis and stratify patients for more intensive follow-up (Figure

56.11). Immunohistochemical evidence of downregulation of parafibromin has a sensitivity of 67% and a specificity of 100% for detecting parathyroid carcinoma and the protein gene product 9.5 (PGP 9.5). Parafibromin immunohistochemistry may be used with immunohistochemistry for PGP 9.5. This is - a protein encoded by ubiquitin carboxyl-terminal esterase LI. It is upregulated in parathyroid carcinoma and has a sensitivity of 78% and a specificity of 100%. All parafibromin-negative and PGP 9.5-positive tumours should be considered for genetic - screening. - - -

Atypical parathyroid tumour Para /f_i bromin Para /f_i bromin NEGATIVE POSITIVE PGP 9.5 PGP 9.5 NEGATIVE POSITIVE High risk of Low risk of Carcinoma malignancy malignancy Figure 56.11 Proposed decision tree for atypical parathyroid tumours using para /f_i bromin and PGP 9.5 immunohistochemistry.

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Accounts for approximately 1% of all cases of PHPT A history of previous neck irradiation remains the only known environmental risk factor The tumours remain dif /f_i cult to diagnose preoperatively as they biochemically resemble PHPT Treatment is focused on controlling hypercalcaemia and removal of the carcinoma where possible Surgery remains the mainstay of treatment for primary presentations and locally recurrent disease. Complete resection of the tumour avoiding spillage is vital in preventing seeding and thus recurrent disease

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Pathology

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The underlying aetiology of PHPT is usually a solitary parathyroid adenoma; however, in a small number of patients (2–4%) there are double adenomas. It may occur in a sporadic fashion or it can be familial (approximately 10%) (MEN type 1, type 4, type 2A or hyperparathyroidism–jaw tumour syndrome [HPT-JT]) in nature. John L Doppman , 1928–2000, radiologist, National Institutes of Health, USA, developed the technique of selective venous sampling for parathyroid localisation. is a history of prior neck irradiation. The underlying genetic pathogenesis of PHPT remains unclear. However, genes r egulating the cell cycle, such as MEN1 and CCND1 , have been recognised as playing an important role owing to the clonal nature of adenomas. Somatic mutations in MEN1 , which encodes menin, occur in 12–35% of sporadic cases and rearrangements or overexpression of CCND1 , which encodes cyclin D1, have been demonstrated in 20–40% of patients. Upregulation of cyclin D may lead to a clonal proliferation within the parathyroid glands. This does not alter the set point of calcium but the hyperplasic nature of the parathyroid cells - themselves causes excessive secretion of PTH. Multigland disease is less common, occurring in approxi - mately 15% of patients. No clinical features di ff erentiate single from multigland disease, although multigland disease is more commonly associated with familial syndromes such as MEN types 1 and 2A, as well as the chronic ingestion of lithium. Pathology

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Permanent hypoparathyroidism

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Permanent hypoparathyroidism is defined as the continuing need for calcium and/or vitamin D replacement at 1 year postoperatively . It is a rare complication when surgery is under taken for PHPT (0.5%), but in secondary hyperparathyroidism it can range from 4% to 12%. Symptoms and signs relate to serum calcium levels. Symptoms include mild circumoral or digital numbness and paraesthesia, carpopedal or laryngeal spasms and cardiac arrhythmias. Chvostek’ s and Trousseau’s signs may be elicited. Chvostek’s sign refers to contraction of the ipsilateral facial muscles on percussion of the facial nerve below the zygoma. Trousseau’s sign refers to the development of carpopedal spasm secondary to occlusion of the arm (usually with a blood pressure cu ff). Biochemical investigations include total and ionised calcium levels as well as serum magnesium levels. An ECG may demonstrate a prolonged QT interval or QRS complex changes. Mild hypocalcaemia can be treated with oral calcium and vitamin D supplementation. Acute symptomatic hypocalcaemia is an emergency and should be corrected with intravenous as well as oral calcium and vitamin D replacement. Traditionally , 10 /uni00A0 mL of 10% calcium gluconate is administered slowly intravenously . Supplemental magnesium may also be required, owing to the synergistic action of transporters for calcium and magnesium. Medical management Medical management is warranted in patients who are deemed unfit or who have contraindications to surgical intervention, in patients with failed surgical intervention or in the long-term management of parathyroid carcinoma. The aims are to prevent skeletal complications (improve bone mineral density and reduce fracture risk) and to stabilise biochemical para meters. There are only limited data on the long-term e ffi cacy of such an approach as surgery is known to provide durable responses. Bisphosphonates/denosumab Bisphosphonates are pyrophosphate analogues that are concentrated in areas of high bone turnover. They inhibit osteoclast activity and apoptosis, thereby increasing bone mineralisation and reducing bone turnover. Studies looking at the management of PHTP utilising bisphosphonates are Frantisek Chvostek , 1835–1884, physician, The Jasefsacademie, Vienna, Austria. Armand Trousseau , 1801–1867, physician, Hôtel Dieu, Paris, France. does appear to stabilise bone mineral density without markedly altering the underlying serum biochemistry . Denosumab is a monoclonal antibody that works as a rece ptor activator of - nuclear factor- κ B (RANK) ligand inhibitor. Data from the DENOCINA trial suggest that it may be a valid treatment option for patients in whom surgery is undesirable. Hormone replacement therapy and selective oestrogen receptor antagonists Hormone replacement therapy (HRT) has been shown to improve bone mineral density and reduce the associated fracture risk in postmenopausal women by reducing bone turnover. Two non-randomised controlled trials have shown a durable and similar response to surgery for PHTP at 4 years, with improvements in bone mineral density but without any improvement in the underlying serum biochemistry . The - rationale for the use of selective oestrogen receptor antag - onists (SERMs) is that they should confer the benefits of HRT but

without the potential adverse vascular and breast e ff ects. The e ff ect on the bone mineral, howev er, appears to be less significant than that of HRT . Calcimimetics The extracellular calcium-sensing receptor on the parathyroid cell surface negatively regulates secretion of PTH. Activation of the receptor decreases secretion of PTH, thereby decreas - ing bone turnover. Calcimimetics, such as cinacalcet, amplify the sensitivity of the calcium-sensing receptor to extracellular calcium, altering the set point and thereby decreasing PTH production. Cinacalcet was approved for use in PHPT by the European Medicines Agency in 2008 and subsequently by the US Food and Drug Administration in 2011 for the treatment of severe hypercalcaemia in patients with PHPT who were unfit for parathyroidectomy . Normalisation of serum calcium levels can be achieved with a similar reduction in the level of PTH, although not to within the normal range. Despite this, neither the urinary calcium nor the bone mineral density appear to change even after 3 years of treatment. Drug toler - ance, especially gastrointestinal side e ff ects, can be problematic and may limit the duration of usage. Permanent hypoparathyroidism

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PHPT is defined as hypercalcaemia in the presence of an unsuppressed and therefore relatively , or absolutely , elevated PTH level. Prevalence of the disease is reported to be 0.2–0.5%, with approximately 100 /uni00A0 000 new cases per year in the USA. The majority of PHPT is sporadic in nature. Familial disease can occur in multiple endocrine neoplasia (MEN) type 1 or type 2A or as a familial cluster. Patients usually present in the fifth or sixth decades and there is a female predominance with a ratio of 3:1. Patients are typically identified incidentally with an elevated total calcium or following routine assessment of bone densitometry (DEXA scan). Most patients will, however some vague constitutional symptoms, such as fatigue, muscle weakness, depression or some mild memory impairment on questioning. The presence of kidney stones remains the most common clinical manifestation of symptomatic PHPT . Between 15% and 20% of patients will have nephrolithiasis and over 40% of patients will have hypercalciuria. Increasingly , postmenopausal women present with significant osteopenia or osteoporosis in the distal one-third of the radius with a minimal reduction in the lumbar spine, which prompts further investigation. This distribution arises as PTH appears to be catabolic at cortical sites (distal one-third of the radius) and anabolic at cancellous sites (lumbar spine). PHPT may present with pancreatitis, although it is rarely seen in patients with milder forms of the disease. Common epidemiologically linked disorders, such as Sir James Paget , 1814–1899, surgical pathologist, Royal College of Surgeons of England. hypertension and peptic ulcer disease, are often encountered. Clinical examination is usually normal. Band keratopathy , pathognomonic of the disease and due to deposition of calcium phosphate crystals in the cornea, is now rarely identified. The di ff erential diagnosis of PHPT includes other causes of hypercalcaemia, which are usually readily distinguishable (Table 56.1). It is important to e xclude the presence of a widespread malignancy , in which patients will typically have other symptoms. The exception to this rule is multiple myeloma, in which hypercalcaemia can be the presenting /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF , have /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

Plasma Ca Parathyroid Parathyroid concentration hormone glands 2+ Activation of Renal tubular Ca mobilised vitamin D absorption from bones 2+ of Ca 2+ Ca absorption in intestine 2+ Plasma Ca concentration Figure 56.2 The actions of parathyroid hormone. TABLE 56.1 Causes of hypercalcaemia. Endocrine Primary hyperparathyroidism Thyrotoxicosis Phaeochromocytoma Renal failure Secondary hyperparathyroidism Tertiary hyperparathyroidism Malignant Skeletal metastatic disease disease Multiple myeloma, lymphoma, leukaemia Solid tumours (PTH-related peptide mediated): lung, renal, squamous cell carcinoma of the head and neck, oesophagus, genital tract Nutritional Excessive vitamin D ingestion Vitamin A intoxication Milk-alkali syndrome Aluminium intoxication Granulomatous Sarcoidosis Tuberculosis Inherited disease Hypercalciuric hypercalcaemia Immobilisation Paget’s disease Drug related Lithium PTH, parathyroid hormone.

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RECURRENT HYPERPARATHYROIDISM

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Recurrent hyperparathyroidism is defined as hypercalcaemia occurring 6 months after surgery but with an intervening period of normocalcaemia. Common causes include missed pathology at the first operation; hyperplasia in remaining or autotransplanted tissue; parathyromatosis; or, very rarely , the development of a second parathyroid adenoma. Parathyro matosis refers to disseminated parathyroid tissue within the rupture of the parathyroid gland during the primary surgery . A definitive indication for surgical intervention must be present prior to embarking on localisa tion studies. Surgical interven - tion will be guided by the radiological imaging. Complication rates of recurrent laryngeal nerve damage and permanent hypocalcaemia are higher in reoperative surgery . RECURRENT HYPERPARATHYROIDISM

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SECONDARY HYPERPARATHYROIDISM

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Secondary hyperparathyroidism is defined as a derangement in calcium homeostasis, which leads to a compensatory increase in PTH secretion. It occurs primarily as a result of chronic kidney disease and is therefore sometimes referred to as renal Daniel Casanova , contemporary , University of Cantabria, Santander, Spain. intestinal malabsorption, vitamin D deficiency , liver disease or - chronic lithium usage. The pathogenesis of secondary hyperparathyroidism is related to renal dysfunction. Abnormalities in the r enal tubu - mild lar absorption of phosphate lead to hyper phosphataemia. This acts directly on the parathyroid cells and stimulates PTH secre - tion. More recent translational research has identified a novel - phosphaturia hor mone, fibroblast growth factor 23 (FGF23). This is progressively secreted from osteocytes to compensate for c hronic phosphate retention that in turn leads to a reduc - tion in 1,25-dihydroxyvitamin D, which by reducing the intes - tinal absorption of calcium also acts to increase secretion of PTH. Previous studies in patients with chronic renal disease - have shown that there is a reduction in the expression of the vitamin D rece ptor and the calcium-sensing receptor, with associated skeletal resistance to PTH. These factors interact - to form the complex pattern leading to progressive secondary hyperparathyroidism in the setting of chronic renal disease. one The pathological characteristics associated with secondary hyperparathyroidism include hyperplasia, asymmetrical glandular enlargement or nodularity . This di ff erentiation is important as, when the parathyroid gland becomes nodular, it loses expression of the vitamin D receptor and the calcium- sensing receptor gene. It has been proposed that nodular or parathyroid glands may be resistant to calcimimetics and therefore refractory to medical management. SECONDARY HYPERPARATHYROIDISM

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SPECIAL CASES Lithium-induced hyperparathyroidism

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- Lithium-induced hyperparathyroidism occurs in 10–15% of patients treated with long-term lithium. It is generally associated with a mild elevation in calcium with failure to suppress PTH. The underlying aetiology can be either gland hyperplasia, with lithium originally thought to stimulate all parathyroid tissue, or a single adenoma, which has been shown to occur in 33–49% of cases. It has recently been suggested that the hyperparathy - roidism may be caused by interference with the parathyroid kinase C signal transduction system and the Wnt pathway . Biochemical abnormalities may resolve with discontinua tion lithium is required or where abnormalities persist following withdrawal of lithium. Minimally invasive surgery is relatively contraindicated in these patients because of the high incidence of multigland disease. Excision, however, should be limited to those glands that are obviously enlarged at exploration rather than a formal three-and-a-half-gland excision. SPECIAL CASES Lithium-induced hyperparathyroidism
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TERTIARY HYPERPARATHYROIDISM

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- Tertiary hyperparathyroidism is a persistent autonomous hypercalcaemic hyperparathyroidism occurring after kidney transplantation. A number of proposed factors may prevent involution of the hyperplastic parathyroid glands following resolution of the underlying renal impairment. These include impaired graft function, non-suppressible PTH secretion, slow involution of enlarged glands or insu ffi cient calcitriol conver - sion by the transplanted kidney . The biochemical diagnosis is confirmed by an elevated - total or ionised calcium, with an associated elevated or unsup - pressed PTH and a reduced phosphate occurring at least 1 year post renal transplantation. Di ff erentiation from PHPT can be di ffi cult. Few er than 1% of patients with tertiary hyperpara - thyroidism will require sur gical intervention (Table 56.5). The only new evidence for intervention is the presence of nodular hyperplasia of the glands themselv es. Traditionally , localisa - tion studies or imaging of the neck was not indicated in tertiary hyperparathyroidism. However, increasing knowledge of the clonal nature of gland h yperplasia suggests that where there is a nodule within the parathyroid with a volume of tissue greater 3 than 500 /uni00A0 mm , then resolution of electrolyte abnormalities is unlikely . /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF The use of calcimimetics in tertiary hyperparathyroidism remains controversial and has not been approved for this indication. However, isolated reports have documented control of hypercalcaemia with minimal side e ff ects in individual patients. Surgical intervention remains the definitive management strategy . Subtotal parathyroidectomy or total

TABLE 56.5 Indications for surgical intervention in tertiary hyperparathyroidism. Subacute severe hypercalcaemia (>3 /uni00A0 mmol/L) Impaired graft function Nodular hyperplasia of the parathyroid gland(s) Progressive symptoms (>2 years following transplantation) Worsening bone disease (pain, fracture, bone loss) Renal stones/nephrocalcinosis Soft-tissue or vascular calci /f_i cations

surgical options. The majority of endocrine surgeons will opt for a subtotal parathyroidectomy in this setting, leaving a gland approximately four times normal in volume to minimise postoperative complications. Total parathyroidectomy without an autograft is not a treatment option because of the postoperative and persistent di ffi culties in managing the associated hypocalcaemia. Summary box 56.3 Tertiary hyperparathyroidism /uni25CF /uni25CF /uni25CF /uni25CF

Persistent autonomous hypercalcaemic hyperparathyroidism occurring after kidney transplantation Diagnosis is made by demonstrating an elevated total or ionised calcium with an associated

elevated or unsuppressed PTH and a reduced phosphate occurring at least 1 year post renal transplantation Localisation studies are not required but a focused neck ultrasonography may con /f_i rm the presence of nodular enlargement Surgical intervention remains the mainstay of treatment and involves a subtotal parathyroidectomy

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