Parathyroid Surgery in Children

6

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This chapter reviews the presentation, diagnosis, and treatment of hyperparathyroidism in children. Compared to adults, parathyroid disease is rare in children and this rarity may lead to delay in diagnosis of the parathyroid problem and delay in recognition of associated conditions. The common causes of hyperparathyroidism, such as parathyroid adenoma and hyperplasia, as well as the less common causes, such as adenocarcinoma, that require a high index of suspicion to diagnose are considered. The chapter will highlight the similarities and differences between children and adults in the diagnosis and management of parathyroid disease.

Incidence/Epidemiology

Hyperparathyroidism (HPT) is a rare disease in children, with an incidence of 2–5 per 100,000, compared to 1 per 1000 in adults [1]. Primary hyperparathyroidism (PHPT), which results from overproduction of parathyroid hormone (PTH), is the most common cause of HPT in both adults and children. A single parathyroid adenoma is the cause of 80–85% PHPT in adults, and is also the most common cause of PHPT in children. Parathyroid hyperplasia of all four glands is responsible for 10–15% of cases of PHPT in adults and is much more common in patients with hereditary conditions such as multiple endocrine neoplasia type 1 (MEN1) [2, 3].

Secondary and tertiary hyperparathyroidism are related to chronic renal failure, which results in continuous stimulation of PTH production, and are less common causes of HPT in children. In pediatric patients with chronic kidney disease (CKD) on dialysis, approximately 80% have secondary hyperparathyroidism with renal osteodystrophy, requiring medical treatment and occasionally surgery.

Parathyroid adenocarcinoma is an exceedingly rare cause of HPT, accounting for less than 1% of all cases of HPT in adults and it is probably even more uncommon in children, although no reports convincingly describe the incidence of parathyroid cancer in the pediatric population [4–9].

As in adults, HPT in children is more common in females than males, with a 3:2 ratio in a retrospective study of 52 pediatric patients [1]. In pediatric patients with sporadic (non-inherited) disease, symptomatic presentation generally occurs between age 15 and 18 years [1, 10]. Patients with MEN syndromes and other inherited forms of the HPT are often diagnosed with hyperparathyroidism earlier than patients with sporadic HPT. Children with inherited HPT might present with symptoms earlier than

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D.J. Ledbetter and P.R.V. Johnson (eds.), *Endocrine Surgery in Children*,
DOI 10.1007/978-3-662-54256-9_6

adolescents with sporadic disease but the earlier diagnosis may be due to screening children who are asymptomatic but have a positive family history or other condition that heightens suspicion for HPT. Earlier detection of abnormal parathyroid glands may also occur in patients with MEN2 during their prophylactic thyroidectomy for medullary thyroid cancer.

Etiology

There are three main forms of hyperparathyroidism: primary, secondary, and tertiary. All three forms result in an overproduction of PTH. Under normal conditions, parathyroid hormone is released in response to decreased serum calcium levels. Increased PTH leads to [1] increased gastrointestinal absorption of calcium via increased renal production of 1, 25-dihydroxy vitamin D_3, [2] osteoclast activation with increased bone breakdown and release of calcium, and [3] increased renal reabsorption of calcium. All of these mechanisms increase serum calcium. Under normal circumstances calcium-sensing receptors (CaSRs) in the parathyroid glands detect the increased serum calcium and activate a negative feedback loop to decrease PTH production [3]. In primary hyperparathyroidism (PHPT), caused by parathyroid adenoma (s), hyperplasia of all four glands, or parathyroid carcinoma, the overproduction of PTH escapes this normal negative feedback loop and hypercalcemia results.

Hyperparathyroidism can manifest in newborns with neonatal severe hyperparathyroidism (NSHPT). This rare disease is associated with severe metabolic bone disease and life-threatening hypercalcemia (often >20 mg/dL) in the first week of life, and must be distinguished from transient neonatal hyperparathyroidism due to maternal hypocalcemia. NSHPT is associated with inactivating mutations in the calcium-sensing receptor genes (*CASR*), which code for the CaSR proteins. Neonates with NSHPT generally have complete or near-complete absence of functioning CaSRs in their parathyroid glands [2]. This results in parathyroid hyperplasia, increased PTH secretion and decreased renal excretion of calcium resulting in severe hypercalcemia [2]. A milder form of this condition results from a monoallelic mutation in *CASR*, which can cause an asymptomatic form of PHPT, termed familial hypocalciuric hypercalcemia (FHH). In these cases, reduced levels of functioning CaSRs result in increased secretion of PTH and modest hypercalcemia that can be managed with medical intervention alone [2].

In some cases of primary HPT, serum calcium levels are in the high-normal range, but PTH levels fail to be appropriately suppressed. This condition is sometimes referred to as "normocalcemic hyperparathyroidism" or "mild hyperparathyroidism." In the rare cases when hyperparathyroidism results from parathyroid carcinoma, patients often have extremely high levels of hypercalcemia (>14 mg/dL), arising from the overproduction of PTH from tumor cells within the parathyroid gland and metastases [4]. These patients can present in hypercalcemic crisis, which is a medical emergency described in more detail in 6.71 Preoperative Management.

Secondary hyperparathyroidism (SHPT) arises in the setting of chronic kidney failure, when vitamin D activation by the kidney declines which reduces gastrointestinal absorption of calcium. In addition, renal excretion of phosphate declines and the increasing serum phosphate binds calcium. Both processes lead to low serum calcium levels that continuously signal the parathyroid glands to produce PTH, resulting in elevated serum PTH levels and ultimately leading to four-gland hyperplasia [3].

Tertiary hyperparathyroidism (THPT) describes the condition in which a parathyroid gland subjected to prolonged stimulation from hypocalcemia, usually due to renal failure or chronic vitamin D deficiency, begins autonomous overproduction of PTH that no longer responds to negative feedback. This can result in higher levels of serum calcium than would be expected from calcium and calcitriol therapy alone [3]. THPT is most often seen after renal transplantation.

Hyperparathyroidism in children can also be a manifestation of MEN1 and MEN2 syndromes.

Parathyroid disease may be the first indicator of MEN disorders and children who present with hyperparathyroidism and have a family history of parathyroid disease or neuroendocrine tumors should undergo genetic testing for the involved genetic mutations (*MEN1* and *RET*, respectively). In MEN1, the *MEN1* gene is a putative tumor suppressor, and the development of MEN1 requires two genetic hits to result in loss of function. One mutation is inherited in the germline and is present in every cell. The second mutation is a sporadic somatic mutation in a single cell of an involved tissue that results in clonal expansion and tumor development. The MEN1 tumor syndrome includes development of parathyroid tumors, pancreatic neuroendocrine neoplasms, pituitary tumors, and bronchial carcinoids [11].

MEN2 syndrome results from an autosomal dominant inheritance of activating mutations in the *RET* proto-oncogene. *RET* (*RE*arranged during *T*ransfection) codes for a receptor tyrosine kinase involved in cellular growth. The missense mutations of the gene result in gain of function alterations in the protein, which manifest as medullary thyroid cancer (MTC) in nearly every patient, as well as varying presence of other endocrine neoplasms [11]. For more information on parathyroid disease in MEN1 and MEN2 please refer to Chaps. 30 and 31, respectively.

Pathology

In children with hyperparathyroidism, as in adults, the most common operative finding is a single adenoma and second most common operative finding is four-gland hyperplasia [1, 12]. In series of children and young adults with PHPT, 60–92% have a single adenoma and 0–40% have four-gland hyperplasia [1, 12, 13]. In a study that focused on patients under 18 years old with no family history of parathyroid or thyroid disease, 100% were found to have single adenomas [13]. Additionally, in a separate series, 10% of patients were found to have ectopic glands, including intrathymic and intrathyroidal adenomas (Fig. 6.1) [1]. On pathologic analysis, specimens show hyperplastic parathyroid tissue.

Adenocarcinoma of the parathyroid is defined by gross or histologic invasion of blood vessels, perineural tissue, thyroid gland, or other surrounding tissues and by the presence of distant metastases. Of note, fibrosis or mitotic figures can be found in adenomas without malignant potential, so these findings are not sufficient to diagnose parathyroid adenocarcinoma [3].

Clinical Presentation

History and Symptoms

Patients with hyperparathyroidism can have a wide range of symptoms, or they can be asymptomatic (Table 6.1) [1, 12]. Pediatric patients are more likely to present with symptoms than adults. While most adult series demonstrate asymptomatic rates of 30–40%, pediatric series report only 0–20% of patients as asymptomatic on presentation [1, 2, 12]. Children are also more likely to present with end organ damage, including pathologic bone fractures, osteitis fibrosa cystica, nephrolithiasis, and pancreatitis [12]. These presentations of advanced disease may be due in part to the frequent delays in diagnosis caused by a low index of suspicion and delay in appropriate confirmatory diagnostic investigations. Hyperparathyroidism is the third most frequent endocrine disease in adults (after diabetes and thyroid disease) [3] and is a commonly considered diagnosis, but in a large series of children and adolescents it took an average of 24 months to diagnose the same disease in pediatric patients [1].

In the rare patients with neonatal severe hyperparathyroidism, symptoms present in the first few days of life and include failure to thrive, hypotonia, respiratory distress, and prominent skeletal involvement. This is always combined with severe hypercalcemia that often requires urgent intervention [2].

A family history of parathyroid disease is common in pediatric patients with HPT, especially in those with genetic disorders such as

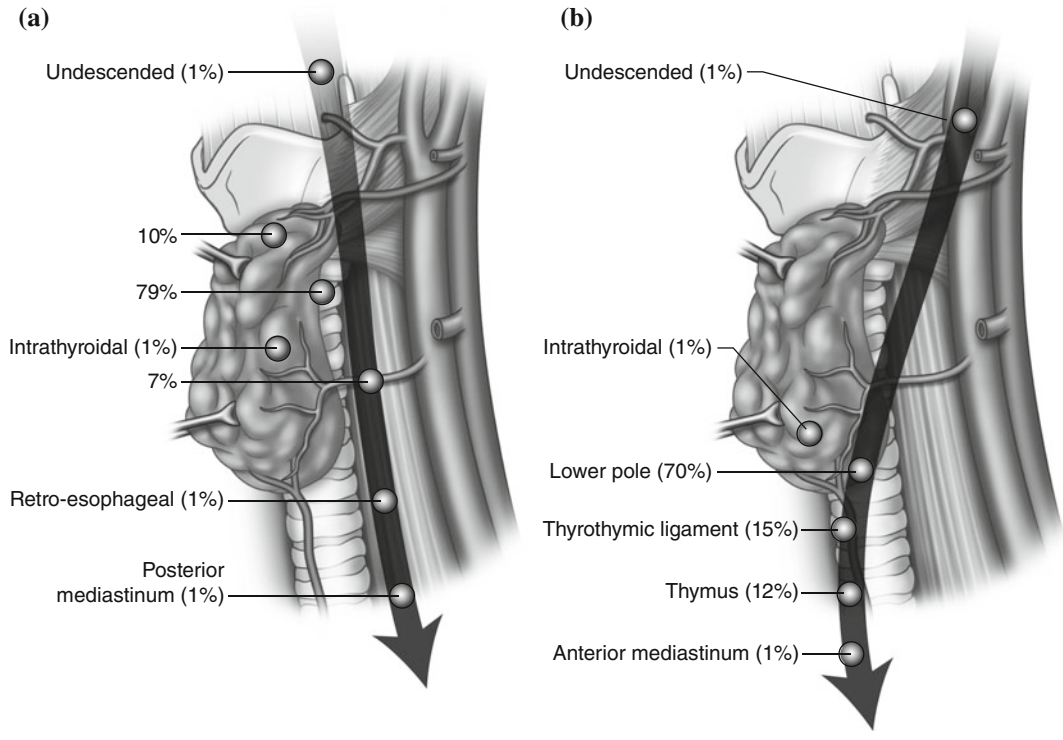

Fig. 6.1 The location and frequency of ectopic superior (**a**) and inferior (**b**) parathyroid glands. The *shaded area* indicates the embryologic of descent of the parathyroid glands

MEN1 or MEN2, or familial HPT. Patients with these inherited conditions are even more likely to present with symptoms when compared to those without a family history [1, 3, 11, 12].

Physical Examination

The physical examination in children and adolescents with HPT is usually normal. The parathyroid glands lie posterior and medial to the lateral border of the thyroid gland (see Chap. 5) and are difficult to palpate even when enlarged. When patients with HPT have palpable neck nodules, the nodules are usually not parathyroid glands [1]. Occasionally an ectopic gland may be palpated as a small (≤ 1 cm), mobile, non-tender neck nodule. Cervical lymph nodes are rarely enlarged and supraclavicular lymph nodes are even more rarely enlarged.

Blood Tests

In any child with suspected hypercalcemia and/or hyperparathyroidism, serum levels of total calcium, PTH, phosphate, and alkaline phosphatase should be checked. Serum TSH levels should be checked to rule out concomitant thyroid disease. Diagnosis of primary HPT is made with elevated PTH levels (>65 pg/mL, though the normal range varies by testing protocol) in the presence of normal or elevated serum calcium (>10.2 mg/dL, though the normal range varies by testing protocol). A PTH level that is not appropriately suppressed with a high-normal serum calcium level is also consistent with HPT. Secondary HPT, in contrast, is diagnosed when elevated PTH levels are present in the setting of hypocalcemia caused by a known separate etiology such as chronic renal failure.

Table 6.1 Clinical presentations of hyperparathyroidism

Asymptomatic
General
• Fatigue
• Weakness
• Myalgias
Neurologic/Psychiatric
• Headache
• Depression
• Cognitive impairment
Skeletal
• Bone pain
• Osteoporosis
• Pathologic fractures
• Osteitis fibrosa cystica
Gastrointestinal
• Anorexia
• Nausea
• Vomiting
• Diarrhea
• Constipation
• Pancreatitis
• Peptic ulcer disease
Renal
• Polyuria
• Polydipsia
• Kidney stones
• Hypertension

Imaging

Preoperative localization of the affected gland is important as it determines the operative approach for parathyroidectomy. If a single enlarged or hyperfunctioning gland is detected, the operation can be performed as a minimally invasive, or unilateral, parathyroidectomy (MIP). Cervical ultrasound (US) can aid both in the diagnosis of parathyroid adenomas and preoperative localization of the diseased gland. Parathyroid adenomas are recognized on ultrasound as a small, round, generally symmetrical, hypoechoic structure (Fig. 6.2). Neck ultrasound is noninvasive, relatively inexpensive, and radiation and sedation can be avoided, but the effectiveness of ultrasound is operator-dependent. Operator dependency probably explains the widely variable published accuracy rates of 48–74% [3, 14]. Ultrasound is also unable to sufficiently evaluate mediastinal glands.

One of the most common and most accurate preoperative localization studies is a dual-phase technitium-99 m sestamibi scan with single-photon emission computed tomography/computed tomography (SPECT/CT) (Fig. 6.3), with accuracy rates over 90% [3, 14, 15]. While the costs of sestamibi imaging with SPECT/CT are higher than ultrasound, this modality is less operator-dependent and is much better at detecting ectopic adenomas. However, when detection rates are based on persistent radionuclide uptake in both phase scans, the false negative rate can be as high as 40%. Recent studies including both adult and pediatric patients show that review of the early phase sestamibi scan by an experienced endocrine surgeon can result in increased preoperative localization of parathyroid adenomas, thus increasing the possibility of performing a MIP [16, 17].

Additional imaging options include CT or magnetic resonance imaging (MRI). CT images rely on the vascularity of parathyroid glands and their relative enhancement with contrast compared to the surrounding structures. CT has a sensitivity of 40–86% depending on the technique and experience of the radiologist [18]. Recently the sensitivity of CT has improved to 88% with the introduction of four-dimensional CT (4D-CT) that utilizes changes in the perfusion of contrast over time in addition to the three-dimensional images [18]. In MRI imaging, hyperfunctioning parathyroid glands show contrast enhancement on T_1-weighted images. Sensitivity for adenoma detection with this modality is 69–88% [18] and it may be preferred in pediatric patients, as there is no associated ionizing radiation and the costs are comparable with sestamibi SPECT/CT [3, 18].

Indications for Operation

The indications for operation vary based on the cause of hyperparathyroidism. In general, published indications derive from primary HPT in adult patients, as this is the most common type of HPT and the disease is uncommon in children. Any patient with elevated or inappropriately normal PTH and symptoms of hypercalcemia, including nephrolithiasis, nephrocalcinosis, renal dysfunction, osteopenia, pathologic fractures, osteitis fibrosa cystica, and altered neurologic function with obtundation, delirium, or coma, should undergo a parathyroidectomy [3, 18].

Regarding patients with asymptomatic PHPT, a National Institutes of Health (NIH) consensus conference published guidelines in 1990 that were amended in 2002 and 2008 [19] that propose surgery should be performed in the following circumstances:

- Serum calcium is more than 1 mg/dL (>0.25 mM/L) above the upper limits of normal.
- Glomerular filtration rate of <60 ml/min (per 1.73 m [2]). Below this level, elevations in serum PTH occur, and pathophysiological abnormalities associated with declining renal function may negatively influence the hyperparathyroid state.
- Reduced bone density, with a Z-score of −2.5 or less in patients younger than 50 years old, or any previous fracture or fragility.
- Age less than 50, as evidence supports a greater risk of complications from PHPT in these individuals over time [19].

Based on these recommendations, all children, adolescents, and young adults diagnosed with PHPT should undergo the appropriate operation to remove the affected gland(s).

If the patient's workup is suspicious for parathyroid carcinoma and the disease appears to be resectable, any biopsy including fine-needle aspiration should be avoided, as this can violate the capsule and increase the risk for tumor implants. The patient should proceed to operative resection, as described below [4].

The indications for operative intervention in secondary hyperparathyroidism are less clear. Medical therapy is the first-line treatment for SHPT, with the goal to increase available serum calcium and vitamin D, decrease hyperphosphatemia, and increase the sensitivity of CaSRs to serum calcium. Medical therapy with calcitriol supplementation and phosphate binders is often

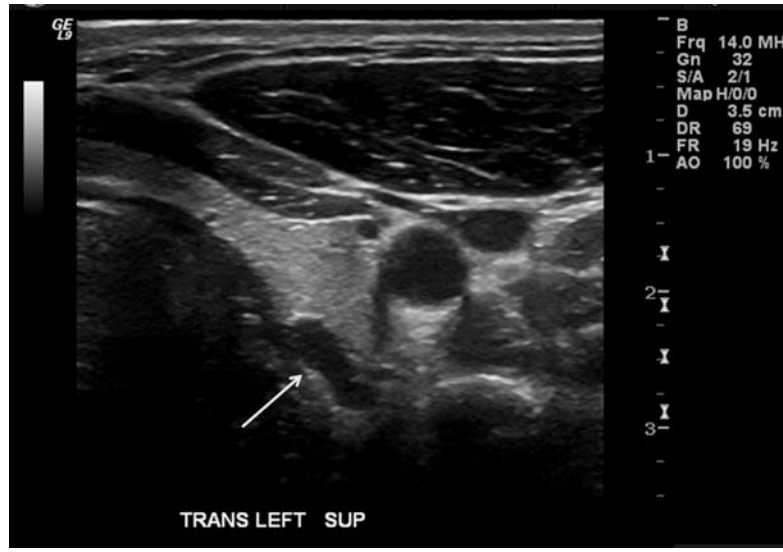

Fig. 6.2 Cervical ultrasound demonstrating a hypoechoic mass (*arrow*) consistent with a parathyroid adenoma posterolateral to the *left* thyroid lobe

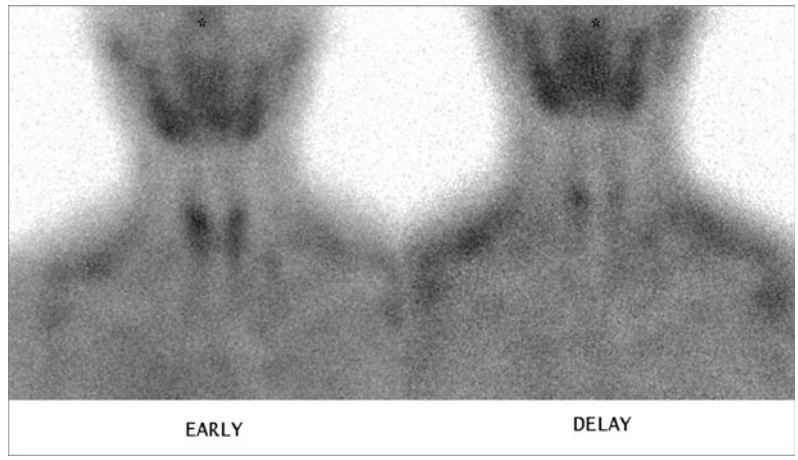

Fig. 6.3 Dual-phase technetium-99 m sestamibi scan showing increased focal uptake of the radionuclide that persists in the late phase scan, indicating a positive localization of a *right side* parathyroid adenoma

sufficient to maintain normal PTH and phosphorous levels. Pilot studies of cinacalcet, a calcimimetic that allosterically activates CaSRs, showed that a single dose predictably lowered serum PTH, calcium, and phosphorous in pediatric renal dialysis patients, which suggests this compound might have further use as medical treatment for pediatric SHPT [20]. Although in most cases calcium and PTH levels return to normal after return of normal renal function surgical treatment of SHPT should be considered in the following circumstances:

- A calcium · phosphate product >70
- Severe bone disease and pain
- Pruritus
- Extensive soft tissue calcification with tumoral calcinosis
- Calciphylaxis [21].

While the vast majority of hyperparathyroidism in the setting of CKD resolves within 6 months of renal transplantation, tertiary hyperparathyroidism (TPHT) develops in 2–3% of patients who receive a renal transplant [22]. Contrary to SHPT, the primary treatment of THPT is surgical. After receiving a kidney transplant patients with SHPT are routinely monitored for resolution of their HPT. Surgical treatment should be considered if any of the following occur after renal transplantation:

- Severe hypercalcemia (>11.5 mg/dL)
- Persistent hypercalcemia (>10.2 mg/dL more than three months after transplant)
- Severe osteopenia
- Symptomatic HPT (fatigue, pruritus, bone pain, pathologic bone fracture, peptic ulcer disease, mental status changes)
- Hypercalcemia with a history of renal calculi [23]

Management

Preoperative Management

The only curative management for PHPT is surgical removal of the diseased parathyroid gland(s). In general, no additional treatment is needed prior to parathyroidectomy. However, as described above, patients with SHPT and THPT are managed medically to control the levels of serum PTH, calcium, and phosphorous, and surgery is only performed if patients meet the indications presented above.

Hypercalcemic Crisis

Occasionally, patients present in hypercalcemic crisis with extremely high levels of serum calcium (generally above 14 mg/dL), oliguria or anuria, and changes in mental status [24]. This is

more common in patients with NSHPT, in part because the syndrome is rare and the initial symptoms go unrecognized. Hypercalcemic crisis is a medical emergency, and patients need to be stabilized before they can undergo a parathyroidectomy. If this is the initial presentation of the patient for hypercalcemia (i.e., they have not previously been diagnosed with HPT), they should undergo a shortened diagnostic workup while they are being medically stabilized. This workup should include:

- History and physical examination
- X-rays of the head, thorax, vertebral column, pelvis, and long bones to look for osteolytic lesions associated with PHPT, metastases, other neoplasms
- Ultrasound examination of the abdominal organs to exclude hepatic, pancreatic, renal, or gynecologic tumors
- Laboratory studies including phosphate, potassium, creatinine, urea, alkaline phosphatase, complete blood count, and PTH [24].

While this workup is taking place, treatment for the severe hypercalcemia should begin. These patients are usually severely dehydrated, and the first step of therapy is intravenous hydration with normal saline. In addition, any medications that are associated with or adversely affected by hypercalcemia should be discontinued. Once intravascular volume is normalized then urinary excretion of calcium is encouraged by additional intravenous fluid. Loop diuretics are added to inhibit calcium reabsorption in the kidney and prevent fluid overload. Patients with renal failure may need urgent hemodialysis. Once the etiology of hypercalcemia is determined to be PHPT, the best definitive treatment is prompt surgical intervention. If surgery cannot be performed urgently, calcium can also be lowered with administration of gallium nitrate, bisphosphonates, or calcitonin, all of which act to inhibit osteoclasts and/or slow bone resorption [3]. However, due to the slow onset of therapeutic effect and long half-life of bisphosphonates, their use can lead to postoperative hypocalcemia, and in general they are not recommended when urgent surgery can be performed. If they are used, it is suggested that, due to children's highly sensitive response to bisphosphonates, only half of the normal dose should be given in the acute setting [25]. Case studies and small pilot studies indicate that cinacalcet, a calcimimetic, may be used in the pediatric population in the short term to lower calcium [20, 26]. Once patients are stabilized, they can proceed to surgery.

Operative Management

The goals of operative care are to identify and remove the diseased parathyroid gland or glands, preserve function in the remaining glands, identify and treat concomitant thyroid disease, and avoid intraoperative complications. The operative approach is determined by considering patient history and results from the preoperative imaging studies. A small series of 25 patients with PHPT demonstrated that patients younger than 18 years old with no family history of parathyroid disease uniformly had single parathyroid adenomas [13].

Parathyroidectomy is conducted either through a bilateral four-gland exploration or as a MIP (Fig. 6.4). For patients with PHPT and preoperative imaging that confirms localization of the diseased gland (as described in 6.54 Imaging), the operation of choice has been MIP. MIP has advantages over bilateral four-gland exploration including decreased operative time, lower hospital costs, shorter lengths of stay, and fewer events of postoperative hypocalcemia [27–32]. An additional benefit of MIP is the unilateral neck exploration, leaving the contralateral side relatively free of manipulation and thus scarring, making future neck operations less difficult. However, controversy around MIP has arisen due to recent large studies in adults with PHPT that indicate long-term recurrence rates may be slightly higher in patients who undergo an MIP versus bilateral exploration [33, 34]. As these findings have not been reported in children and postoperative complication rates are often higher in children than in adults [35], our center continues to

perform MIPs in pediatric patients with positive preoperative localization studies. In this procedure, a small (1.5–2 cm) incision is made along an anterior neck skin fold on the side of midline identified with preoperative imaging, and unilateral exploration is completed to identify both ipsilateral parathyroid glands, taking care to identify and protect the recurrent laryngeal nerve. If an enlarged gland is encountered, it is removed and intraoperative testing modalities described below are used to confirm that the excised gland is the causative adenoma [3]. If no enlarged gland is identified, this procedure can be converted to a bilateral exploration without extension of the incision. If it is found that the patient has four-gland hyperplasia, a subtotal parathyroidectomy can be performed, with removal of 3.5 glands and an intended remnant amount of 50–75 mg. In these cases, we recommend cryopreservation of parathyroid tissue for later autotransplantation if the patient goes on to have postoperative hypoparathyroidism.

The success of MIP is enhanced with intraoperative localization adjuncts, including radioguidance and intraoperative PTH values. A radio-guided parathyroidectomy involves preoperative intravenous injection of technetium-99 m sestamibi 1–2 h prior to the operation and use of a hand-held gamma probe intraoperatively to localize hyperfunctioning parathyroid glands. Once the gland is removed, an ex vivo radionuclide count greater than 20% of background counts indicates appropriate removal of hyperfunctioning parathyroid tissue. This technique has been shown to be equally effective in children as in adults despite smaller adenomas in children [36].

Intraoperative PTH (ioPTH) monitoring is a reliable, accurate adjunct to a successful MIP [37]. After induction of anesthesia and prior to making an incision, a baseline PTH level is drawn. Once the enlarged gland is removed, a rapid PTH serum level is checked at 5, 10 and 15 min post removal. A fall in the serum PTH level to below 50% of baseline at any of these time points is indicative of cure, and the operation can be concluded. However, if the levels fail to fall by 50%, the presence of a second hyperfunctioning gland should be suspected, and cervical exploration should be continued. If a second adenoma is found and removed, this process of ioPTH measurement is repeated. In some cases, the first ioPTH shows an increase above the baseline level. This increase is attributed to manipulation of the gland during the exploration. By treating the elevated first ioPTH value as the new baseline and monitoring for a drop of later ioPTH levels by 50% below this new baseline, cure can still be accurately detected [38]. Using ioPTH decline as measurement for cure can be used effectively in children. In fact, a study of the kinetics of PTH decline in 15 pediatric patients with PHPT suggests that their serum PTH falls faster than in adults after removal of a parathyroid adenoma and 100% demonstrated cure with the 5 min ioPTH level, compared to 54% of adults by 5 min and 70% by 10 min [10]. This suggests that, in a child with PHPT, a persistently elevated ioPTH level at 5 min indicates presence of additional hyperfunctioning parathyroid tissue and operative exploration should continue in an effort to identify it.

The operative approach to SHPT assumes four-gland hyperplasia pathology, and begins with bilateral exploration. If hyperplasia indeed is present, a subtotal parathyroidectomy or total (four glands) parathyroidectomy with autotransplant is performed. A study of 105 patients undergoing parathyroidectomy for SHPT or THPT showed that ioPTH monitoring is still useful in patients as it can demonstrate cure [39]. This study gives even more striking rationale for using ioPTH monitoring in parathyroidectomy for THPT. While patients with THPT are generally assumed to have hyperplasia as well, if only one or two glands are noted to be enlarged during a bilateral exploration, these should be removed and ioPTH values should be checked. Limited resection with only one or two glands was sufficient for cure in 21% of patients with THPT [39]. Additionally, ioPTH monitoring allowed for the detection of supernumerary glands in three patients with THPT, meaning the surgical approach was altered in a total of 25% of THPT patients based on ioPTH results [39].

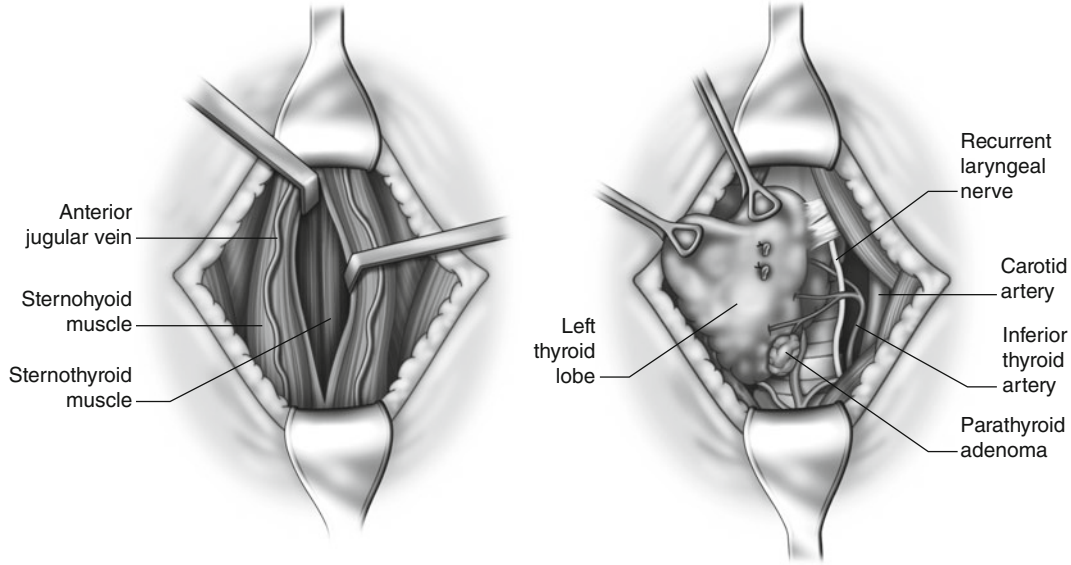

Fig. 6.4 Minimally invasive parathyroidectomy (MIP). A 1.5–2 cm transverse skin incision is made in line with the skin folds. The anterior strap muscles (sternohyoid, sternothyroid) are separated, and a unilateral exploration is undertaken to identify both ipsilateral parathyroid glands. The enlarged gland is removed, taking care to protect the recurrent laryngeal nerve

In patients with parathyroid carcinoma and no evidence of metastases, the recommended procedure is *en bloc* removal of the parathyroid cancer, with ipsilateral thyroid lobectomy, isthmectomy, tracheal skeletonization, excision of any adherent muscle, and a central lymph node dissection if deemed appropriate based on appearance and extension of the primary tumor and surrounding nodes [4]. Parathyroid carcinomas are often difficult to diagnose preoperatively, especially in children where the index of suspicion is exceedingly low. Therefore, if certain gross features, such as firm texture, thick gray or white capsule, and adherence to surrounding tissue, are encountered during the operation, the surgeon should consider carcinoma [4]. Utmost care must be taken to not violate the capsule so as to prevent spillage. Once *en bloc* resection has been performed, exploration of the remaining glands should be completed as carcinoma can coexist with multiple gland disease [4]. If the disease is metastatic, resection of the primary disease and the metastases can improve PTH and hypercalcemia [4].

Postoperative Management

In our practice, patients older than age 14 with an uneventful procedure and no comorbidities are discharged to home on the same day as their operation. Patients younger than age 10 can be admitted to the general care floor overnight with a general diet and full activity. When a patient falls between those ages, individual patient characteristics and parental comfort level are taken into account to decide whether or not to admit them to the floor postoperatively. Patients and parents are educated about the signs and symptoms of hypocalcemia, and patients are discharged with calcium carbonate (Tums), 1000–3000 mg based on age (Calcium carbonate dosing—Age 2–5 yrs: 400 mg, maximum 1200 mg daily; Age 5–11 yrs: 800 mg, maximum 2400), to be used as needed for hypocalcemia. If patients are at high risk for postoperative hypocalcemia (e.g., subtotal parathyroidectomy, redo operation), or if the patient and family would have difficulty detecting symptoms of hypocalcemia, they are

discharged on 1000–3000 mg scheduled daily. Patients who undergo a total parathyroidectomy with forearm transplant of parathyroid tissue will require complete calcium and calcitriol replacement at discharge because the autograft will not become fully functional for at least 2 weeks. Patients return for a follow-up appointment one week postoperatively.

Complications

Multiple studies have indicated that high-volume endocrine surgeons have better clinical outcomes with fewer complications [35, 40, 41]. Operative complications include recurrent laryngeal nerve damage, which can cause hoarseness with unilateral injury or airway compromise if both nerves are damaged. In adults, recurrent laryngeal nerve monitors are sometimes used. These utilize a special endotracheal tube with a built-in sensor that is too large to use in most children, and thus they are not used in pediatric parathyroidectomies. Another possible complication is hematoma, though this risk is much lower than in thyroidectomy. Similarly, wound infections are possible but uncommon complications. Parathyroidectomy is considered a clean procedure and thus perioperative antibiotic prophylaxis is not recommended. If a wound infection does occur, conservative treatment with antibiotics should be attempted prior to open drainage. Due to the location of the incision on the neck, many delicate underlying structures are exposed with an open wound, and this should be prevented if possible.

Hypoparathyroidism can result from devascularization or removal of the remaining parathyroid glands and can lead to hypocalcemia. This is often transient, with symptoms resolving within the first week postoperatively. The risk of both transient and permanent hypocalcemia is higher in subtotal parathyroidectomy and in reoperative parathyroidectomy. For these reasons, it is recommended to cryopreserve some of the removed parathyroid tissue for potential autotransplantation should the patient's hypoparathyroidism persist. A study of the Healthcare Cost and Utilization Project—National Inpatient Sample demonstrated that children having parathyroidectomy have higher complication rates than adults, both general (21% vs. 12%) and endocrine-specific complications (15.2% vs. 6.2%) [35]. Age affects complication rates as well, with more complications in children age 0–6 (22%) than in those aged 7–12 (1.1%) or 13–17 (0.6%) [35]. This supports the involvement of multidisciplinary care with pediatric endocrine patients, especially in the youngest subset.

Long-Term Outcomes and Follow-up

In HPT, disease persistence is defined as elevated serum calcium within 6 months postoperatively, and disease recurrence denotes initially normal serum calcium levels that become elevated again more than 6 months postoperatively. Cure is defined based on calcium levels and not PTH levels because PTH levels can remain elevated postoperatively in 20–30% of patients. The scarce data available on cure rates and recurrence rates in pediatric patients suggest they are similar to those in adults, with 96–100% cured in reported series [1, 12, 13]. Patients should continue follow-up with their primary care provider or endocrinologist with routine monitoring for symptoms of hypercalcemia. While less than 5% will have persistent disease or develop recurrent disease, these few may require reoperative parathyroidectomy. The most common cause of persistent HPT is surgeon inexperience in locating and adequately excising the parathyroid adenomas [42].

Recurrent HPT is uncommon, but occurs more frequently in the setting of familial disease. When recurrent or persistent disease is suspected, a full workup must be completed to confirm the diagnosis. When the diagnosis is confirmed, vocal cord assessment should be performed to evaluate for occult dysfunction [42, 43]. Surgeons considering reoperative parathyroid surgery should have a higher threshold for operation than initial surgery due to the increased difficulty of reoperation. These include markedly elevated

serum calcium level, recurrent nephrolithiasis, or ongoing bone loss. Patients should undergo preoperative imaging, and the operative approach must be decided based on the findings with the consideration that the diseased gland has a higher chance of being in an ectopic location. The use of intraoperative localization adjuncts is especially important in reoperative parathyroidectomies [43].

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