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Parathyroid Surgery in Children

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Introduction

This review of parathyroid surgery in children will briefly discuss parathyroid gland embryology and anatomy before focusing on the pathophysiology, clinical presentation, and treatment of hyperparathyroidism in children. Compared to adults, parathyroid disease is rare in children. This rarity means that the principles of caring for children with parathyroid disease are largely extrapolated from the richer adult experience, however the unique pediatric aspects of parathyroid problems and their surgical treatment will be considered.

Parathyroid embryology and anatomy

Parathyroid glands arise from the endoderm of the pharyngeal pouches in weeks 5 to 6 of gestation. The inferior parathyroid glands originate from the higher third pharyngeal pouches and the superior glands originate from the lower fourth pharyngeal pouches. In week 7 of gestation the parathyroid glands begin to migrate with the thyroid and thymus caudally and medially to their final position in the lower neck. During normal migration the inferior glands pass beyond the superior glands and end up on the dorsal surface of the lower pole of the thyroid or slightly more caudal in the thyrothymic ligament or adjacent thymus. The normal migration of the superior parathyroid glands is shorter and their final position on the posterior surface of the upper pole of the thyroid is more constant than the final position of inferior parathyroid glands (1).

Ectopic parathyroid glands result from abnormal migration. With incomplete migration the superior parathyroid gland can end up anywhere from the posterior pharynx to just above the upper pole of the thyroid. In another pattern of abnormal migration the superior parathyroid glands can join the ultimobranchial body as it fuses with the median thyroid resulting in an intrathyroidal parathyroid gland. The inferior parathyroid gland has an even wider spectrum of possible ectopic positions. With incomplete migration it may end up in the neck along the

carotid sheath from the angle of mandible to the lower pole of the thyroid. Excessive migration results in the parathyroid gland in the thymus or anterior mediastinum (1).

Grossly, normal parathyroid glands are small, each roughly 5 x 3 x 1 mm and weighting 35 to 40 mg. They have a fine capsule and are supplied by a single vascular pedicle typically arising from branches of the inferior thyroid artery (1). Histologically, parathyroid glands contain two main cell types - chief cells and oxyphil cells. The more numerous chief cells are small neuroendocrine cells with secretory granules containing parathyroid hormone (PTH). Oxyphil cells are larger than chief cells with a smaller, darker nucleus and relatively larger amount of cytoplasm. The function of oxyphil cells is not clear.

Parathyroid physiology

The parathyroid gland is intimately involved with calcium homeostasis. Chief cells have a plasma membrane calcium-sensing receptor that detects extracellular calcium and activates a negative feedback loop to decrease PTH production when extracellular calcium rises. PTH is an 84 amino acid peptide with a short half-life of only 2–5 minutes. PTH raises extracellular calcium by increasing gastrointestinal absorption of calcium via renal activation of vitamin D, by activating osteoclasts that breakdown bone and release calcium stores, and by increasing renal tubular reabsorption of calcium (1).

Hyperparathyroidism

Hyperparathyroidism (HPT) is the overproduction of PTH and it is rare in children. The incidence of HPT in children is only 2–5 per 100,000 compared an incidence of 1 per 1,000 in adults (2). In both adults and children HPT is more common in females than males, with a 3:2 ratio in a report of 52 pediatric patients (2). Hyperparathyroidism may be primary, secondary, and tertiary.

Primary HPT is the most common cause of HPT in both adults and children and may be caused by parathyroid adenomas (usually single, but occasionally multiple), four gland hyperplasia, or, rarely, by parathyroid carcinoma. In all causes of primary HPT the overproduction of PTH escapes the normal negative feedback loop and hypercalcemia results. In adults, primary HPT is usually the result of a single parathyroid adenoma (80–85%) or hyperplasia of all four glands (10–15%) (1). In children and young adults with primary HPT, 60–92% have a single adenoma and 0–40% have four-gland hyperplasia (2–4). In both adults and children with primary HPT four gland hyperplasia is more common in patients with hereditary conditions such as Multiple Endocrine Neoplasia Type 1 (MEN1) (1, 5)

Patients with hyperparathyroidism can have a wide range of symptoms, or they can be asymptomatic (see Table 1)(2, 4). Children are more likely to be symptomatic than adults. In most adult series 30–40% of patients are asymptomatic at presentation while in pediatric series only 0–20% of patients are asymptomatic at presentation (2, 4, 5). Children are also more likely to present with end organ damage, including pathologic bone fractures, osteitis fibrosa cystica, nephrolithiasis, and pancreatitis (4). These presentations of advanced disease may be due in part to the frequent delays in diagnosis commonly in pediatric series. In one

large series children and adolescents were symptomatic an average of 24 months before diagnosis (2).

Children with sporadic (non-inherited) primary HPT usually present with symptoms between age 15 and 18 years (2). Patients with MEN syndromes and other inherited forms of the HPT are often diagnosed earlier than patients with sporadic HPT. It is not clear if this earlier diagnosis is because these patients develop symptoms at an earlier age or because a higher index of suspicion leads to earlier screening when there is a high-risk family history. Earlier detection of abnormal parathyroid glands may also occur in patients with MEN2 during their prophylactic thyroidectomy for medullary thyroid cancer.

Parathyroid adenocarcinoma is a rare cause of primary HPT. It accounts for less than 1% of cases of HPT in adults and it is probably even rarer in children, although the precise incidence of parathyroid cancer in the pediatric population is unknown (6–8).

Adenocarcinoma of the parathyroid is defined by gross or histologic invasion of blood vessels, perineural tissue, thyroid gland, or other surrounding tissues, or by the presence of distant metastases. Fibrosis or mitotic figures can be found in adenomas without malignancy, so these findings alone are not sufficient to diagnose parathyroid adenocarcinoma. (1) Patients with parathyroid adenocarcinoma have PTH production from the tumor and any metastases and may present with extreme hypercalcemia (calcium levels >14 mg/dL) and hypercalcemic crisis.

A unique pediatric presentation of primary HPT is Neonatal Severe Hyperparathyroidism (NSHPT). NSHPT is associated with inactivating mutations in the calcium-sensing receptor genes. Neonates with NSHPT have complete or near-complete absence of functioning calcium-sensing receptors with resulting parathyroid hyperplasia, unregulated PTH secretion, and severe hypercalcemia (5). This rare disease presents in the first few days of life with failure to thrive, hypotonia, and respiratory distress. Evaluation reveals marked, sometimes life-threatening hypercalcemia (often >20 mg/dL) and severe metabolic bone disease. NSHPT must be distinguished from transient neonatal hyperparathyroidism due to maternal hypocalcemia. A milder form of NSHPT results from a monoallelic mutation in the calcium-sensing receptor genes and can result an asymptomatic form of primary HPT, known as familial hypocalciuric hypercalcemia (FHH) (5). In FHH reduced levels of calcium-sensing receptors result in modest elevation of PTH and mild hypercalcemia that can be managed with medical intervention alone (5).

Secondary HPT is seen in patients with chronic renal failure and reduced vitamin D activation by the kidney with a resulting decrease in gastrointestinal absorption of calcium. These patients also have a reduced renal excretion of phosphate and the resulting excess of serum phosphate binds calcium. Both mechanisms lead to low serum calcium levels that continuously signal the parathyroid glands to produce PTH, resulting in elevated serum PTH levels. Chronic overstimulation ultimately leads to four-gland hyperplasia (1). Approximately 80% of children on dialysis have secondary HPT that requires medical treatment and occasionally surgery.

Tertiary HPT 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. Even when calcium levels raise to normal or higher the glands of tertiary HPT no longer respond to negative feedback and continue autonomous production of PTH. Tertiary HPT is most often seen after patients with renal failure and secondary HPT have a kidney transplant and return of renal function.

Preoperative evaluation

The diagnosis of primary HPT is made when either symptomatic or asymptomatic patients are found to have hypercalcemia and elevated PTH levels. A PTH level that is not appropriately suppressed with a high-normal serum calcium level is also consistent with primary HPT. Secondary HPT, in contrast, is diagnosed when elevated PTH levels are present in the setting of hypocalcemia caused by renal failure or other condition. As in adults, the physical examination of children and adolescents with HPT is usually normal. Parathyroid glands are normally located posterior and medial to the lateral border of the thyroid gland and even when enlarged are usually not palpable. When patients with HPT have palpable neck nodules on physical exam the nodules are usually not parathyroid glands (2). Other laboratory evaluation in patients with primary HPT should include serum TSH to rule out concomitant thyroid disease and since primary HPT in children can be the first manifestation of MEN1 and MEN2 syndromes, any child who presents with hyperparathyroidism and has a family history of parathyroid disease or neuroendocrine tumors should have genetic testing for the mutations of *MEN1* and *RET*.

Preoperative imaging of patients with primary HPT has become important since localization of the abnormal parathyroid gland(s) can determine the operative approach for parathyroidectomy. If a single abnormal, enlarged or hyperfunctioning gland is detected, it can be assumed to be a single adenoma and removed with a minimally invasive, or unilateral, parathyroidectomy (MIP). When a single abnormal gland cannot be localized preoperatively or when the patient is suspected to have parathyroid hyperplasia then four-gland, or bilateral exploration is performed.

Cervical ultrasound may visualize a parathyroid adenoma as a small, round, generally symmetrical, hypoechoic structure. Since ultrasound is non-invasive, relatively inexpensive, avoids radiation, and can be performed without sedation even in children it may be the first step in the imaging evaluation of HPT. However, the effectiveness of ultrasound is dependent upon the experience and proficiency of the sonographer. Operator-dependency probably explains the widely variable (48–74%) diagnostic accuracy reported for ultrasound localization of parathyroid adenomas (9). Another disadvantage of ultrasound is the inability to localize ectopic parathyroid glands in the mediastinum.

Another preoperative localization study is the dual-phase technetium-99m sestamibi scan with single-photon emission computed tomography/computed tomography (SPECT/CT). While the costs of sestamibi imaging with SPECT/CT are higher than ultrasound, it is less operator dependent, much better at detecting ectopic adenomas, and has accuracy rates of over 90% (9, 10). 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 and increase the chances of performing a MIP (11, 12).

Additional imaging options for preoperative localization include CT or magnetic resonance imaging (MRI). Parathyroid glands may be seen on CT because of their vascularity and 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 (13). The sensitivity of CT may be improved to 88% with 4-dimensional CT that visualizes changes in perfusion over time in addition to the 3-dimensional images (13). Hyperfunctioning parathyroid glands on MRI show contrast enhancement on T₁-weighted images. Sensitivity for adenoma detection with MRI is 69–88% (13) and it may be preferred in pediatric patients since there is no associated ionizing radiation and the costs are comparable with sestamibi SPECT/CT (13).

Indications for operation

Recommendations for parathyroidectomy for primary HPT are derived from adult experience. There is general agreement that patients with elevated or inappropriately normal PTH and symptoms of hypercalcemia such as nephrolithiasis, nephrocalcinosis, renal dysfunction, osteopenia, pathologic fractures, osteitis fibrosa cystica, or altered mental status should have parathyroidectomy (13). For asymptomatic patients with primary HPT a National Institutes of Health (NIH) consensus conference published guidelines for surgery in 1990 that were updated in 2002 and 2008 (14). The guidelines are notable that they recommend parathyroidectomy for patients with primary HPT who are less than 50 years of age because the long term risks of the disease are greater than the risks of surgery (14). Based on these recommendations, all children, adolescents, and young adults diagnosed with primary HPT should have surgery.

The indications for operative intervention in secondary HPT are less clear. Medical treatment with calcium, vitamin D, and phosphate binders is usually successful in maintaining normal PTH and phosphorous levels. In addition, pilot studies of cinacalcet, a calcimimetic that allosterically activates calcium-sensor receptors have shown that a single dose predictably lowers PTH, calcium, and phosphorous in pediatric renal dialysis patients suggesting that it might be useful for children with secondary HPT (15). Surgical treatment of secondary HPT should be considered if the calcium phosphate product is greater than 70 or if there is severe bone disease, uncontrolled pruritus, extensive soft tissue calcification with tumoral calcinosis, or calciphylaxis (16).

In contrast to secondary HPT, the primary treatment of tertiary HPT is surgical. Although the vast majority of patients with renal insufficiency and secondary HPT who have a successful kidney transplant will have normal calcium homeostasis within 6 months, tertiary HPT develops in 2–3% (17). Patients who have a kidney transplant are routinely monitored for resolution of their secondary HPT. Surgical treatment should be considered if hypercalcemia is severe (>11.5 mg/dL) or persistent (calcium >10.2 mg/dL more than three

months after transplant) or if it is associated with severe osteopenia, a history of renal calculi, or symptoms of HPT including fatigue, pruritus, bone pain, pathologic bone fracture, peptic ulcer disease, or mental status changes (16).

Parathyroidectomy

The operative goals of parathyroidectomy for HPT are to remove the abnormal parathyroid gland(s), preserve the normal glands, treat associated thyroid disease, and avoid complications. Parathyroidectomy may be performed via a bilateral 4-gland exploration or as a MIP. The operative approach is determined by the patient's history and preoperative imaging studies. The history can often predict whether or not a patient has an adenoma or hyperplasia. For example, in a small series of 25 patients with primary HPT who were younger than 18 years and had no family history of parathyroid disease all had a single adenoma (3). The additional importance of localization is apparent from another series that found that 10% of patients had ectopic glands, including intrathyroidal and intrathyroidal adenomas (2).

For patients with primary HPT and preoperative imaging that localizes the abnormal gland our operation of choice has been MIP. MIP has advantages over bilateral 4-gland exploration including decreased operative time, lower hospital costs, shorter lengths of stay, and fewer episodes of postoperative hypocalcemia (18–23). Another potential benefit of MIP is the unilateral neck exploration that leaves the contralateral side relatively free of scarring and makes future neck operations less difficult. However, adults with primary HPT have slightly higher long-term recurrence rates with MIP than traditional bilateral exploration (24, 25). Despite this potential disadvantage we continue to perform MIPs in pediatric patients with positive preoperative localization studies since the slightly higher recurrence rate has not been reported in children and since complication rates of parathyroidectomy are higher in children than in adults (26).

A MIP consists of a small (1.5–2 cm) incision in an anterior neck skin fold on the side of midline identified by preoperative imaging and then a unilateral exploration identifying both parathyroid glands on that side, taking care to identify and protect the recurrent laryngeal nerve. If an enlarged gland is encountered, it is removed and then either intraoperative radioguidance or intraoperative PTH testing is done to confirm that the excised gland is the causative adenoma (1). If no enlarged gland is identified then the MIP is converted to a bilateral exploration. If a patient is found to have four-gland hyperplasia, a subtotal parathyroidectomy can be performed, with removal of 3.5 glands and leaving a remnant of 50–75 mg. In these patients, we recommend cryopreservation of parathyroid tissue for possible later autotransplantation if the patient develops persistent postoperative hypoparathyroidism.

The success of MIP can be improved with techniques such as radioguidance and intraoperative PTH (ioPTH) monitoring that confirm the intraoperative localization of abnormal glands (27). A radioguided parathyroidectomy involves preoperative intravenous injection of technetium-99m sestamibi 1–2 hours 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 (28).

With ioPTH monitoring a baseline PTH level is determined after induction of anesthesia just prior to making an incision. PTH levels are checked again 5, 10, and 15 minutes after the enlarged gland is removed. A fall of the serum PTH level to below 50% of the baseline value at any of these time points indicates a curative resection and the exploration is concluded. However, if the levels do not decrease by 50%, then another hyperfunctioning gland should be sought. When other abnormal glands are found then PTH levels are again measured. In some cases, the first ioPTH may increase above the baseline level, presumably due to manipulation of the gland during the exploration. By treating the elevated initial 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 predicted (29). Using ioPTH decline to confirm adequate cure has been used effectively in children and the fall may be more dramatic. This was suggested by our experience of ioPTH monitoring in 15 pediatric patients with primary HPT that showed that 100% of the children demonstrated cure with the 5 minutes ioPTH determination while only 54% of adults demonstrate cure at 5 minutes and 70% demonstrate cure by 10 minutes (30).

The operative approach to secondary HPT assumes four-gland hyperplasia, and begins with bilateral exploration. If hyperplasia is present, a subtotal parathyroidectomy, as described above, or a total parathyroidectomy with removal of all four glands and autotransplant of a small remnant in the forearm is performed. A study of 105 patients having parathyroidectomy for secondary HPT or tertiary HPT showed that ioPTH monitoring can also demonstrate cure in these patients (16). This finding was notable because although patients with tertiary HPT are generally assumed to have hyperplasia, if only one or two glands are noted to be enlarged during a bilateral exploration, then these should be removed and ioPTH levels should be checked. Limited resection with only one or two enlarged glands was sufficient to cure 21% of patients with tertiary HPT (16). Additionally, ioPTH monitoring allowed for the detection of supernumerary glands in 3 patients with tertiary HPT, meaning the surgical approach was altered by ioPTH result in 25% of tertiary HPT patients in this series (16).

Postoperative Care

In our practice, older adolescents are treated as adults and often discharged to home on the same day if the operation is uneventful and there are co-morbidities. Younger patients, especially those younger than 10 years of age or those who may be unable or unreliable to report symptoms of hypocalcemia are often observed overnight, although not restricted in diet or activity. Patients and parents are educated about the signs and symptoms of hypocalcemia, and patients are discharged with oral calcium carbonate to be used as needed. Patients who have a subtotal parathyroidectomy or redo operation are at high risk for postoperative hypocalcemia and usually need to be observed postoperatively. Routine, scheduled oral calcium carbonate is prescribed postoperatively for these high-risk patients

and if the patient and family would have difficulty detecting symptoms of hypocalcemia. 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 take at least 2 weeks to become functional.

Outcomes

After surgery for HPT the outcome is defined by long-term calcium levels rather than PTH levels because PTH levels can remain elevated despite normal calcium levels. Patients with normal calcium levels over the long-term are said to be cured. The outcomes of pediatric patients after parathyroidectomy for HPT are similar to adults, with 96–100% cured in reported series (2–4).

Disease persistence is defined as when the serum calcium remains elevated after an operation or when it initially normalizes and then becomes abnormally high again within 6 months of an operation. The most common cause of persistent HPT is surgeon inexperience in locating and adequately excising the parathyroid adenomas (31).

Disease recurrence is defined as when the serum calcium level normalizes after an operation only to become elevated again more than 6 months postoperatively. 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 (31, 32). Surgeons considering reoperative parathyroid surgery should have a higher threshold for operation than initial surgery due to the increased difficulty of reoperation and increased risk of complications. Indications for reoperation include markedly elevated serum calcium level, recurrent nephrolithiasis, or ongoing bone loss. Patients should undergo preoperative imaging, and the operative approach must be chosen based on the imaging findings and the knowledge that there is a higher risk that the diseased gland is in an ectopic location. The use of intraoperative localization adjuncts is especially important in reoperative parathyroidectomy (32).

In addition to disease persistence or recurrence other complications of parathyroidectomy include recurrent laryngeal nerve injury, bleeding, infection, and postoperative hypoparathyroidism and hypocalcemia. Recurrent laryngeal nerve injury can result in hoarseness with unilateral injury or airway compromise if both nerves are damaged. Recurrent laryngeal nerve monitors are sometimes used intraoperatively in an effort to aid identification of the nerve and prevent injury. These monitors consist of a special endotracheal tube with a built-in sensor. Unfortunately, they are not always available in the sizes needed for children. Another possible complication is bleeding and neck hematoma although this risk is much lower than with thyroidectomy. Wound infections are also uncommon after parathyroidectomy. It is considered a clean procedure and perioperative antibiotic prophylaxis is not recommended. Hypoparathyroidism can result from devascularization or removal of the remaining parathyroid glands and can lead to hypocalcemia. The hypocalcemia is often transient, with symptoms resolving within the first week postoperatively. The risk of both transient and permanent hypocalcemia is higher after

subtotal parathyroidectomy and reoperative parathyroidectomy. For these reasons it is recommended to cryopreserve part of the resected parathyroid tissue in these circumstances for potential autotransplantation should the patient suffer persistent hypoparathyroidism.

Children are at higher risk of complications from parathyroidectomy than adults. 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%) (26). The risk for complications is related to age with more complications in younger children - 22% in children younger than 7 years, 1.1% in children aged 7–12 years and only 0.6% in those 13–17 years of age (26). Since multiple studies of parathyroidectomy in adults have indicated that high-volume endocrine surgeons produce better clinical outcomes with fewer complications (26, 33) and since the youngest and smallest children are most likely to benefit from pediatric specialty care the ideal care for children with parathyroid disease is likely to be delivered by multi-disciplinary teams of adult and pediatric specialists in settings with the resources to care for children.

Long-term follow up

Children who have a parathyroidectomy for HPT require life-long monitoring for symptoms of recurrent hypercalcemia and possible disease recurrence. Depending upon the circumstances they might require regular determinations of serum calcium. Extrapolating from adult data, it is thought that less than 5% of patients will have persistent disease or develop recurrent disease and possibly require reoperative parathyroidectomy. However, it is difficult to be certain of the course of the disease in any individual child. The uncertainty is due to the rarity of hyperparathyroidism in children, the lack of understanding of the molecular pathogenesis of hyperparathyroidism, and the paucity of long term follow up data available for those who suffer the disease in childhood.

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Table 1

Clinical presentations of hyperparathyroidism

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