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Parathyroid conditions in childhood

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ABSTRACT

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. Hyperparathyroidism (HPT) is the overproduction of PTH and it is rare in children, with an incidence of 2-5 per 100,000. 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, including presentation, imaging, operative approach, and complications, will be considered.

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 5–6 weeks 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 the 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 the 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 the mandible to the lower pole of the thyroid. Excessive migration results in the parathyroid gland in the thymus or the anterior mediastinum.[1]

Grossly, normal parathyroid glands are small, each roughly 5 × 3 × 1 mm and weighing 35–40 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—the chief cells and the oxyphil cells. The more numerous chief cells are small neuroendocrine cells with secretory granules containing the parathyroid hormone (PTH). Oxyphil cells are larger than the 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 min. PTH raises extracellular calcium by increasing gastrointestinal absorption of calcium via renal

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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 with an incidence of 1 per 1000 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), by 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 the 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 (Table).[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 a 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 the ages of 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.

Table
Clinical presentations of hyperparathyroidism.

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

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 from 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 that is 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 rise 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 after 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 level of normal serum calcium is also consistent with primary HPT. Secondary HPT, by contrast, is diagnosed when elevated PTH levels are present in the setting of hypocalcemia caused by renal failure or other conditions. As in adults, the physical examination of children and adolescents with HPT is usually normal. The parathyroid glands are normally located posterior and medial to the lateral border of the thyroid gland, and even when enlarged they are usually not palpable. When patients with HPT have palpable neck nodules on physical