Chapter 14
Primary Hyperparathyroidism in Children and Adolescents

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Case Presentation

A 13-year-old previously healthy boy was referred for evaluation and treatment of hypercalcemia. His laboratory tests were calcium 11.5 mg/dL (9.6–10.6 mg/dL), parathyroid hormone (PTH) 121 pg/mL (15–65 pg/mL), phosphorus 3.7 mg/dL (4.0–5.2 mg/dL), and creatinine 0.7 mg/dL (0.4–0.8 mg/dL). He consumed approximately 1,000–1,200 mg of calcium daily through his diet. Growth and development had been normal. He had no history of fractures, nephrolithiasis, and no symptoms attributable to hypercalcemia. His urine calcium was elevated at 358 mg/day (5.8 mg/kg/day; nl – <4 mg/kg/day). X-ray of the

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kidney, ureters, and bladder (KUB) did not identify occult kidney stone disease.

Laboratory assessment was performed due to a history of familial isolated primary hyperparathyroidism (FIPHPT). His father, older sister, and multiple additional paternal family members had undergone parathyroid surgery for PHPT. The underlying genetic cause for FIPHPT was unknown. There was no family history of pituitary disease, pancreatic/duodenal tumors, medullary thyroid cancer, adrenal tumors, or jaw tumors.

Six months later, his serum calcium increased to 12.5 mg/dL with a PTH of 163 pg/mL. He remained asymptomatic with no fractures or clinical renal disease. His calcitonin was normal as was his 24-h urine catecholamines and metanephrines. No jaw tumors were noted on physical exam.

Assessment and Diagnosis

Primary hyperparathyroidism (PHPT) is a commonly encountered endocrine disorder in adults, the incidence of which appeared to have increased after the introduction of automated serum calcium measurements in the 1970s, with another peak observed in the 1990s which coincided with the sharp increase in bone mineral density measurement. The overall incidence in adults reported from 1998 to 2010 was 50.4 per 100,000 person years [1, 2]. However, it is still a rare condition in infants and children with an incidence estimated at only 2–5 per 100,000 [3, 4]. Although some studies of children have suggested a male [5, 6] or female preponderance [3, 7], a recent review found no significant sexual predilection in children [4]. This is in contrast to the clear preponderance of disease in women in the adult population. Although PHPT is most commonly caused by a single adenoma in both children and adults, one study found that 31 % of children had familial disease which is in contrast to the

small fraction of adults who have familial PHPT [3, 4]. As in adults, children with familial disease are much more likely to have parathyroid hyperplasia rather than a single adenoma. It is therefore critical to consider the family history when evaluating any child with PHPT.

Several germline gene defects have been identified that can lead to familial PHPT (Table 14.1) [4]. Neonatal severe hyperparathyroidism (NSPHPT) is a distinct form of PHPT caused by biallelic mutations in the *CASR* gene which encodes the calcium-sensing receptor, a G-protein-coupled receptor on the plasma membrane of parathyroid and renal tubule cells. Affected neonates may have severe metabolic bone disease and life-threatening hypercalcemia within the first few days of life, often requiring urgent intervention [4, 6, 8]. In contrast, heterozygous *CASR* mutations causing familial hypocalciuric hypercalcemia (FHH) typically lead to a mild and generally asymptomatic hypercalcemia [4, 8]. Multiple endocrine neoplasia type 1 (MEN1), a syndrome characterized by parathyroid, pancreatic, and pituitary tumors, is the most common cause of inherited PHPT. More than 90 % of MEN 1 patients will have PHPT, more commonly multiple adenomas or diffuse hyperplasia, and it is usually the first manifestation of the syndrome. Less common genetic syndromes causing PHPT include MEN2a, with 20–30 % of the patients developing PHPT, and hyperparathyroidism-jaw tumor (HPT-JT) syndrome, a rare autosomal dominant syndrome due to mutations in the *HRPT2* gene which is characterized by parathyroid adenomas and fibro-osseous lesions of the maxilla and mandible [4].

Elevated serum calcium with an elevated or inappropriately normal PTH is the hallmark biochemical feature that establishes the diagnosis of PHPT in children. This must be distinguished from secondary HPT that is commonly due to vitamin D and or calcium deficiency leading to elevated PTH concentrations with low-normal or low serum calcium levels. When evaluating a child with hypercalcemia, it is important to be aware that the normal ranges for serum calcium and phosphorus differ based on

Table 14.1 Clinical features of genetic syndromes associated with primary hyperparathyroidism

	MEN 1	MEN 2a	NSHPT/FHH	HPT-JT	FIHP
Clinical features	PHPT Pancreatic/duodenal tumors Pituitary tumors (functioning and nonfunctioning) Skin findings (angiofibromas, collagenomas)	PHPT Medullary thyroid carcinoma Pheochromocytoma	PHPT Severe hypercalcemia in NSHPT Mild hypercalcemia in FHH Low urine calcium	PHPT Fibro-osseous jaw tumors Uterine tumors Renal tumors	PHPT
Genes affected	*MENIN*	*RET*	*CaSR*	*HRPT2/CDC73*	

MEN multiple endocrine neoplasia, *NSHPT* neonatal severe hyperparathyroidism, *FHH* familial hypocalciuric hypercalcemia, *HPT-JT* hyperparathyroidism-jaw tumor syndrome, *FIHP* familial isolated hyperparathyroidism, *PHPT* primary hyperparathyroidism

age and gender (Table 14.2). Healthy infants and children have higher calcium and phosphorus concentrations compared to adults. This finding will influence the interpretation of laboratory studies, especially in children with mild calcium and parathyroid abnormalities. Urine calcium should also be interpreted with the age of the child in mind. Older children can often provide a 24-h urine sample in which case an upper limit of normal of 4 mg/kg/day can be applied. In infants and younger children, a calcium-to-creatine ratio on a spot urine sample can be used (Table 14.2). Some patients may also have hypophosphatemia, due to the action of PTH in the kidney and an elevated serum alkaline phosphatase, especially with documented bone involvement.

A recent review of the biochemical profile of children and adolescents with PHPT found a greater degree of hypercalcemia and hypercalciuria at presentation compared to adults despite similar parathyroid hormone concentrations. Furthermore, adenoma weight and alkaline phosphatase activity among age groups did not reveal significant difference. These observations suggest a possible greater sensitivity of target organs to PTH and an apparent decrease in the sensitivity of the parathyroid adenoma to negative feedback by calcium in young patients with PHPT [4, 9].

PHPT (especially sporadic) in children is associated with greater morbidity and end-organ damage at the time of diagnosis compared to adults. Most modern-day adult cohorts are asymptomatic and diagnosed incidentally [4, 9, 10], while as many as 79–91 % of children with PHPT present with symptoms attributable to the disease [3, 7, 11]. Another significant difference of juvenile compared with adult PHPT is the presence of end-organ damage at the time of diagnosis, the most common of which are renal and skeletal involvement [3, 11]. Bone disease, presenting as bone pain, radiographic evidence of osteopenia and osteolysis, diminished bone densitometry or fractures, occurs in about 43 % of children. Nephrolithiasis or nephrocalcinosis, at times leading to chronic kidney disease, is present in about 39 % [3, 4, 11].

Table 14.2 Age- and gender-appropriate normal values

	Normal values
Serum total calcium, males	
1–14 years	9.6–10.6 mg/dL
15–16 years	9.5–10.5 mg/dL
17–18 years	9.5–10.4 mg/dL
19–21 years	9.3–10.3 mg/dL
≥22 years	8.9–10.1 mg/dL
Serum total calcium, females	
1–11 years	9.6–10.6 mg/dL
12–14 years	9.5–10.4 mg/dL
15–18 years	9.1–10.3 mg/dL
≥19 years	8.9–10.1 mg/dL
Serum inorganic phosphorus, males	
1–4 years	4.3–5.4 mg/dL
5–13 years	3.7–5.4 mg/dL
14–15 years	3.5–5.3 mg/dL
16–17 years	3.1–4.7 mg/dL
≥18 years	2.5–4.5 mg/dL
Serum inorganic phosphorus, females	
1–7 years	4.3–5.4 mg/dL
8–13 years	4.0–5.2 mg/dL
14–15 years	3.5–4.9 mg/dL
16–17 years	3.1–4.7 mg/dL
≥18 years	2.5–4.5 mg/dL
Random urine calcium/creatinine ratio	
0–12 months	<2,100 mg/g
13–24 months	<450 mg/g
25 months–5 years	<350 mg/g
6–10 years	<300 mg/g
11–18 years	<260 mg/g
≥19 years	<220 mg/g

The normal values listed above were adapted from Mayo Medical Laboratories. Each laboratory may have different reference values

Nonspecific symptoms such as fatigue, poor appetite, weight loss, depression, hypertension, polyuria, polydipsia, abdominal pain, nausea, and vomiting may be the only manifestations of the disease or they may be associated with end-organ damage [3, 4, 11]. About 15 % of patients were asymptomatic at the time of diagnosis and were only discovered following an incidental finding of hypercalcemia [4]. This distinct clinical history of PHPT in children and adolescents may be attributed to several factors. Because routine biochemical screening is not performed as commonly in children as in adults, a degree of ascertainment bias may arise. As such, a diagnosis of PHPT is made only when the disease becomes symptomatic which is more reminiscent of PHPT in adults prior to the routine measurement of serum calcium [1, 12, 13]. Lack of specific symptoms may also lead to a delay in the appropriate diagnosis in many patients. The average delay occurring between the onset of symptoms and diagnosis ranges from 7.2 months to as long as 4.7 years in children [3, 7, 14]. Patients without renal symptoms had a longer duration of symptoms before a diagnosis of PHPT was secured. This significant delay in diagnosis unfortunately leads to more end-organ damage in this population.

Surgery is the only definitive treatment for PHPT and is the mainstay of management in pediatric patients. Currently, there are no existing guidelines on the management of asymptomatic children with PHPT. However, they have a higher potential to present with end-organ damage compared to adults [7]. Furthermore, a study that observed the natural history of asymptomatic adult patients who did not undergo surgery revealed progression of the disease in one third of the subjects over a 15-year follow-up [15]. Little information is available regarding the changes in skeletal and renal outcomes in children after parathyroidectomy. A single case report described a pronounced improvement in bone density after parathyroidectomy in a 16-year-old boy [16]. Resolution of renal stone disease has been reported in some children with persistent disease noted in others [7, 16]. The current consensus is that all asymptomatic adults

less than 50 years of age should be considered for surgery [10]. It is therefore prudent to perform surgery in the pediatric population even if they have mild disease.

Surgical outcome in pediatric patients is generally excellent, with successful restoration of normal serum calcium in 94 % of cases [3]. This parallels previously reported success rates in adults [3, 17]. Short-term complications include postoperative transient hypocalcemia, musculoskeletal symptoms, and transient vocal cord paralysis. Long-term adverse events such as permanent vocal cord dysfunction or hypoparathyroidism are uncommon when performed by an experienced endocrine surgeon. Several reports have concluded that the incidence of complications, length of hospital stay, and cost correlates to surgeon volume, with superior outcomes observed among high-volume endocrine surgeons [18, 19].

Management

The patient underwent a parathyroid scan that revealed a clear left-sided parathyroid lesion (Fig. 14.1a). At surgery, a left superior 620 mg parathyroid gland was removed. Because of the family history, the left inferior parathyroid gland (30 mg) was also removed so as to avoid the need for future left neck exploration. Both glands were noted to be hypercellular. Four months after surgery, his serum calcium and parathyroid hormone concentrations were normal. Fifteen months after his initial surgery, he was found to have recurrent hyperparathyroidism with a serum calcium of 11.5 mg/dL, phosphorus of 2.7 mg/dL, creatinine of 0.8 mg/dL, and PTH of 79 pg/mL. His urine calcium was significantly elevated at 446 mg/day (7.3 mg/kg/day). Renal ultrasound did not identify nephrolithiasis or nephrocalcinosis.

His bone density measured by dual-energy x-ray absorptiometry (DXA) was normal. A parathyroid scan was obtained revealing a clear parathyroid lesion on the right (Fig. 14.1b). A second operation was undertaken and a 210 mg hypercellular right superior parathyroid gland was removed.

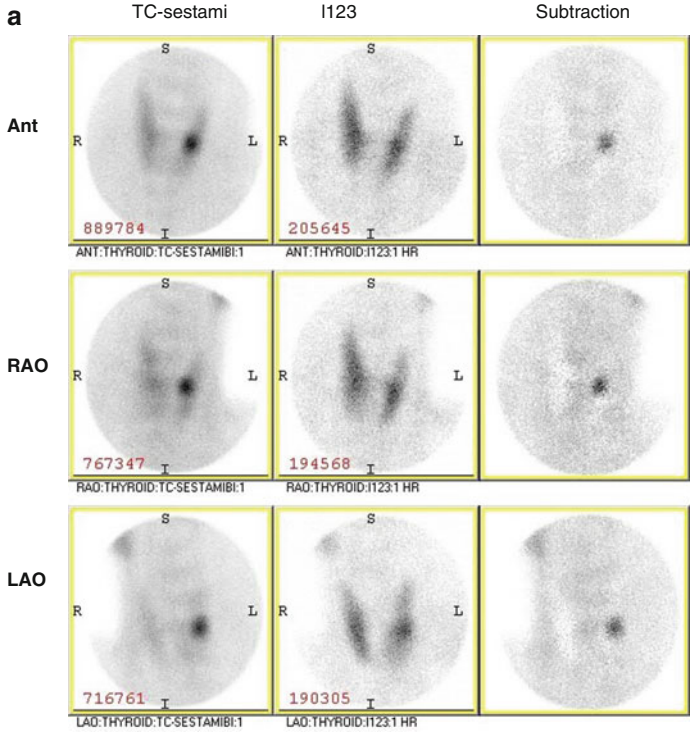

Fig. 14.1 Dual isotope parathyroid scan of the patient (**a**) at the time of diagnosis and (**b**) 15 months after the initial surgery

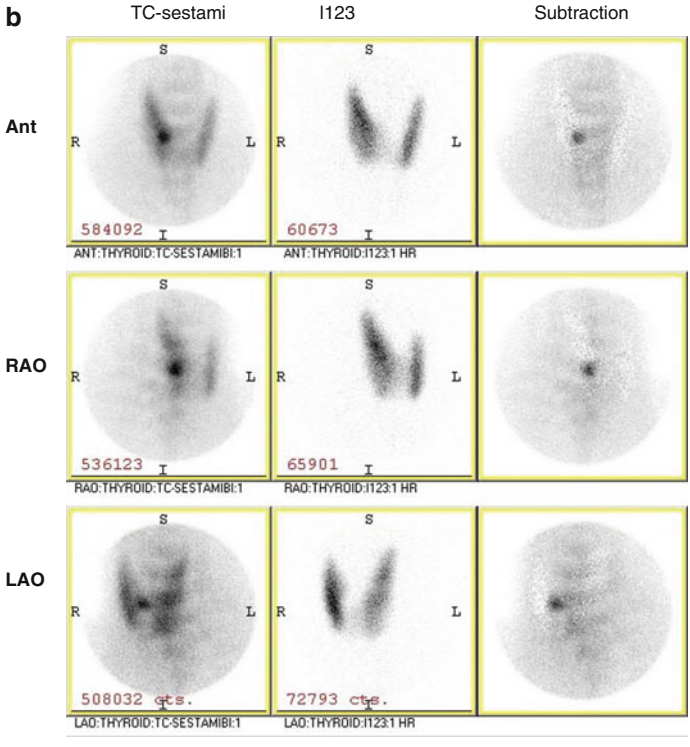

Fig. 14.1 (Continued)

Outcome

The patient recovered well from his second surgery without complications. He remains asymptomatic with normal serum calcium and parathyroid hormone concentrations 4 years after his second surgery.

Conflict of Interest All authors state that they have no conflicts of interest.

Clinical Pearls/Pitfalls

- Symptomatic disease with end-organ damage is common in children with PHPT.
- A detailed family history should be obtained for all children with PHPT and genetic disorders considered, especially in those with multi-gland disease/hyperplasia.
- Surgery should be undertaken by high-volume surgeons with experience in performing endocrine surgery in children.
- Age-appropriate normal ranges for serum calcium should be used when considering the diagnosis of hyperparathyroidism in children.

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