Rapid Correction of Bone Mass after Parathyroidectomy in an Adolescent with Primary Hyperparathyroidism

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Context: Primary hyperparathyroidism is rare in children. Absence of specific symptoms and limited biochemical evaluation in children has led to lengthy delays in diagnosis with the potential for damage to the kidneys and skeleton.

Setting: The setting involved a private practice referral to a large tertiary care center.

Patients: Our patient is a 16-yr-old male presenting with gross hematuria, left flank pain, and right foot pain.

Intervention(s): A biochemical evaluation revealed hypercalcemia and elevated parathyroid hormone levels. Renal ultrasonography demonstrated bilateral nephrolithiasis. Parathyroid ultrasonography and dual-phase technetium-99m sestamibi scintigraphy revealed a parathyroid adenoma in the left mid/lower anterior thyroid bed. A 4.5-g adenoma was removed at parathyroidectomy.

Main Outcome Measure(s): Bone mineral content and density performed by dual energy X-ray absorptiometry at the time of diagnosis and 1 yr after parathyroidectomy.

Results: The main outcome measurement is a dramatic (24%-whole body and 49.9%-left hip) increase in bone mineral density during the 1-yr interval.

Conclusions: Delay in diagnosis of hyperparathyroidism is common in children, related to vague symptomatology and infrequent use of laboratory evaluations in children. Such delays lead to increased risk of osteoporotic fractures and kidney stones. This case illustrates the emergent need of diagnostic evaluation in children presenting with similar symptoms. We emphasize the importance of bone densitometry in children, which is not often considered as part of the standard evaluation in this age group. The remarkable increase in bone mineral density in the 1 yr after surgery attests to the plasticity of recovery of the growing skeleton. (J Clin Endocrinol Metab 96: E347–E350, 2011)

Primary hyperparathyroidism is a rare disease in children, with an incidence of two to five in 100,000 (1). Children have presented with a variety of nonspecific symptoms such as neuromuscular weakness, mental status changes, nausea and vomiting, weight loss, and constipation (2). The lack of specific symptoms in children has led to lengthy delays in diagnosis, usually exceeding 2 yr (1) but reported as long as 4.7 yr (3). In severe disease, presenting symptoms have included bone pain, polydipsia, polyuria, renal colic, and urolithiasis (4), indicating that severe renal and skeletal manifestations may be evident at diagnosis. Moreover, eye findings, including band keratopathy (calcium deposits in the cornea), have been described in children at diagnosis.

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Abbreviations: BMD, Bone mineral density; DXA, dual-energy x-ray absorptiometry; 99mTc MIBI, technetium sestamibi.
End organ damage is common in pediatric patients with primary hyperparathyroidism (5). The incidence of nephrocalcinosis in children with parathyroid adenomas is reported to be between 30% and 70% (6), and bone involvement is reported in up to 80% (5). Skeletal findings reported in 6–70% of patients have included subperiosteal resorption, osteopenia, kyphosis, resorption of the digital tufts and lamina dura, slipped capital femoral epiphysis, pathological fractures, and brown tumors (5).

We describe an adolescent male who presented with a history of hematuria and multiple fractures. Bone densitometry evaluation by dual-energy x-ray absorptiometry (DXA) revealed markedly reduced bone mineral density (BMD) (whole body Z-score less than 3.5 SD for age). The cortically enriched hip BMD (Z-score = −3.2) was relatively less dense than spine BMD (Z-score = −2.2), suggesting greater effects of excess parathyroid hormone exposure on cortical than trabecular bone, typical of the expected changes in adults with hyperparathyroidism (7).

**Case Reports**

In 2008, a 16-yr-old boy presented with gross hematuria and 4–5 wk of left flank pain, coincident with right foot pain that was attributed to a radiologically diagnosed stress fracture of his right heel. He described an isolated occurrence of gross hematuria 4 yr before the current presentation, as well as three long bone fractures over the previous 10 yr, believed to have resulted from sports injuries. These included fractures of the right tibia (1998), left distal tibia (2003), right distal radius (2007), and the recent right calcaneus stress fracture. The arm fracture in 2007 was described by the treating orthopedist as “slow to heal.” Urologic evaluation and urinary tract imaging by computed tomography at the time of the initial episode of hematuria was unremarkable. A diagnosis of sports-related renal contusion was made, and no further diagnosis was pursued.

Family history revealed no other endocrine or orthopedic abnormalities. Specifically, there was no history of family members with hematuria, kidney stones, or osteoporosis. The patient took no medications and had no known drug allergies. Physical examination at 16 and 3/12 yr revealed a height of 170.0 cm (30th centile, based on CDC stature-for-age and weight-for-age percentiles), weight of 48.4 kg, (5th centile), with a body mass index of 16.7. These growth percentiles were consistent throughout the previous 5 yr. His physical examination revealed Tanner IV pubertal staging (Table 1). He was referred immediately for management of hypercalcemia and surgery.

Renal ultrasonography demonstrated multiple bilateral kidney stones with hydronephrosis of the left kidney. After lithotripsy, the stone was determined to consist of calcium oxalate. Biochemical investigation revealed hypercalcemia (13.8 mg/dl, 3.45 mmol/liter), hypophosphatemia (2.2 mg/dl, 0.71 mmol/liter), mildly elevated serum alkaline phosphate activity (461 U/liter), elevated circulating 1,25 dihydroxy vitamin D (136 pg/ml, 353.6 pmol/liter), and a serum intact PTH level of 859 pg/ml; leading to a diagnosis of primary hyperparathyroidism (Table 1). He was referred immediately for management of hyperparathyroidism and surgery.

Upon hospital admission, he was hydrated with normal saline, and underwent ultrasound (Fig. 1A) and dual-phase 99mTc sestamibi (99mTc MIBI) parathyroid scintigraphy. Twenty millicuries of 99mTc MIBI was injected intravenously, and 15 min after the injection, a 180° anterior planar image of the neck and chest was obtained, followed by a single proton emission computerized tomography (SPECT) of the region demonstrating an intense focus

### TABLE 1. Serum biochemistry

|                       | 1 month before PTX | At PTX | 1 wk after PTX | 1 month after PTX | 1 yr postsurgery | 2 yr postsurgery |
|-----------------------|--------------------|-------|---------------|-------------------|------------------|------------------|
| Calcium (8.8–10.2 mg/dl)$^a$ | 13.8               | 14.0  | 9.6           | 8.5               | 9.2              | 9.5              |
| Phosphorus (2.5–4.5 mg/dl) | 2.2                | 2.1   | 5.1           | 4.2               | 4.2              | 2.1              |
| Mg (1.5–2.5 mg/dl)     | 1.9                | 1.8   | 0.6           | 0.6               | 130              | 2.496            |
| Alk Phos (48–230 U/liter) | 461               | 502   | 4             | 8                 | 8                | 8                |
| Creatinine (0.5–1.3 mg/dl) | 0.68              | 0.6   | 35            | 23                | 32               | 4                |
| Intact PTH (10–69 pg/ml) | 859               | 714   | 4             | 8                 | 8                | 8                |
| Mid-molecule PTH (10–25 NLeq/ml) | 17            | 17    | 17            | 17                | 17               | 17               |
| 25-OH vitamin D (20–45 ng/ml) | 0.25             | 0.25  | 0.25          | 0.25              | 0.25             | 0.25             |
| 1,25 (OH)$_2$D (27–71 pg/ml) | 136            | 136   | 136           | 136               | 136              | 136              |

Conversion to SI units: calcium, mg/dl × 0.25 = mmol/liter; phosphorus, mg/dl × 0.323 = mmol/liter; Mg, mg/dl × 0.411 = mmol/liter; creatinine, mg/dl × 88.4 = μmol/liter; 25-OH vitamin D, ng/mL × 2.496 = mmol/liter; 1,25 (OH)$_2$D, pg/ml × 2.6 = pmol/ml. PTX, Parathyroidectomy; Alk Phos, serum alkaline phosphorus activity.

$^a$ Quest Laboratories.

$^b$ Reference ranges are shown in parentheses.
in the left mid/lower thyroid bed anteriorly. Delayed imaging was performed 120 min postinjection.

These studies revealed a parathyroid adenoma in the left mid/lower anterior thyroid bed, with no ectopic focus. DXA (Hologic QDR 4500W bone densitometer, Z-scores determined by Hologic software using age-related normative data) revealed marked reduction in BMD for age with Z-scores of the lumbar spine, left hip, and whole body of -2.2, -3.2 and -3.9, respectively (Fig. 1, B–D).

The 4,500-mg left parathyroid adenoma was excised 4 d later. Intraoperative PTH sampling demonstrated a baseline value of 670 pg/ml (reference range 10–65), and a 20-min post-resection value of 53 pg/ml, consistent with the hypersecreting source of PTH. Histologic examination revealed a benign cellular lesion, and immunostaining showed a proliferation index of less than 10%, consistent with a benign adenomatous lesion.

The preoperative circulating 25-hydroxyvitamin D level (17 ng/ml, 42.4 nmol/l) was sufficient to avoid severe postoperative hypocalcemia; supplementation was withheld until after surgery as not to exacerbate preoperative hypercalcemia. The patient experienced mild numbness and tingling of his extremities in the setting of normal serum calcium but no overt tetany. He was instructed to take 1500 mg of elemental calcium daily upon hospital discharge.

Serum calcium levels remained in the low to normal range in the month after surgery (Table 1), accompanied by occasional mild symptoms of neuromuscular irritability, perhaps attributable to a slight reduction in parathyroid reserve. Thus, calcium supplementation was continued for several months.

One year following surgery, at 17 and 3/12, his height was 176.2 cm (50th centile for age); his weight was 64.8 kg (47th centile for age), and his body mass index was 20.9 at Tanner stage V. DXA was performed 1 yr after parathyroidectomy on the identical densitometer. In contrast to the typical 5% increase in BMD for an individual of this age (8), a quite dramatic increase in BMD was evident, particularly in the cortically enriched hip site (Fig. 1, B–D). The increase in lumbar spine, left hip, right forearm, and whole body BMD over the year after parathyroidectomy was 28.1%, 49.9%, 28.6%, and 24.3%, respectively. In contrast, although the patient continued to demonstrate linear growth, the increase in height was only 3.6%. Bone mineral content Z-scores were comparably improved, with lumbar spine increasing from -1.8 to +0.5 and whole body increasing from -3.8 to -1.5.

Repeat renal ultrasonography demonstrated resolution of all remaining kidney stones by 18 months after surgery, and 24-h urine calcium excretion was within normal limits (100 mg/24 h; 1.5 mg/kg/24 h) as was his calcium-creatinine ratio (0.052 mg/mg, non-fasting).

**Discussion**

A delay in diagnosis of hyperparathyroidism, as observed in this case, is not unusual in children. This finding may be related to vague presenting symptoms, the infrequency of laboratory evaluation in children presenting with nonspecific complaints such as fatigue, weakness, and weight loss (5), and the rarity of the disease in this age group. Hematuria in children, while uncommon, should prompt an evaluation of hyperparathyroidism, including renal ultrasonography and biochemical evaluation of blood and urine. The identification of hypercalcemia and elevated
circulating PTH should prompt further investigations. Specifically, imaging of the parathyroid glands using ultrasound or $^{99m}$Tc MIBI (5) should be performed. Bone densitometry should be performed, and selective skeletal radiography may be indicated. Others have identified band keratopathy in children by slit lamp examination. Early diagnosis and treatment of primary hyperparathyroidism in children is key to preventing end organ damage. 

DXA is widely used in the assessment of bone mass in children. Despite limitations in providing true volumetric BMD, its widespread availability, speed, and minimal radiation exposure have resulted in increasing use in children. The availability of pediatric reference data (9) has further made the interpretation of this technique more useful in the clinical setting (10). However in most reported cases of childhood primary hyperparathyroidism, DXA has not been widely used to evaluate the degree of bone mineral deficit or the recovery of bone mass following treatment. It is notable that studies in adults that examined changes in bone mass after parathyroidectomy demonstrate a much less significant recovery. In a series that examined 44 patients, average age of 56 yr, annual percent increases in lumbar and radial BMD 1 yr after parathyroidectomy were 12.2 ± 1.4% and 11.6 ± 1.6%, respectively (11). By contrast, our patient’s recovery was far more pronounced at 28.1% in the lumbar spine and 28.6% in the right forearm in the year after parathyroidectomy.

Finally our patient did show an increase in height and weight percentiles 1 yr after surgery. This may be related to continuation of adolescent growth after a period of growth retardation. It is interesting to speculate that long-term severe hyperparathyroidism may have contributed to this growth retardation.

As illustrated in this case, the severity of osteoporosis followed by the rapid improvement in BMD to nearly normal values further emphasizes the value of early diagnosis and treatment of primary hyperparathyroidism to avoid severe end organ damage.

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