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Clinical report

Primary hyperparathyroidism in Thai children: case series and literature review

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Background: Primary hyperparathyroidism is a common disease in adults, but extremely rare in the pediatric age group. To our knowledge, pediatric primary hyperparathyroidism has never been reported in Thailand.
Objectives: To describe 3 cases of primary hyperparathyroidism presenting in Thai children with different clinical manifestations.
Methods: Cases of primary hyperparathyroidism in 3 Thai pediatric patients are reported herein, with a brief literature review.
Results: Three patients are described. The first patient, a 14-year-old Thai girl, presented with progressively worsening bowlegs and lordosis of the spine for 1.5 years. The second patient, a 15-year-old Thai boy, presented with a history of hip pain and constipation for 3 years. The third patient, an obese 11-year-old Thai boy, presented with acute abdominal pain, which was initially incorrectly diagnosed as acute pancreatitis.
Conclusions: The clinical symptoms of hyperparathyroidism in Thai children are nonspecific at an early stage of the disease. The diagnoses are usually delayed and the patients therefore suffer complications of long-term hypercalcemia such as bone deformities or renal nephrocalcinosis. We recommend initial laboratory screening in pediatric patients with nonspecific symptoms and complaints of persistent bone pain. Appropriate investigations to confirm or eliminate primary hyperparathyroidism should be made, as an early diagnosis can facilitate early treatment and prevent the organ damage that can result from delayed diagnosis.

Keywords: Hypercalcemia, hyperparathyroidism, parathyroid adenoma, parathyroid hyperplasia

Primary hyperparathyroidism (pHP) is extremely rare in children with an estimated prevalence of 2–5 in 100,000, mostly in adolescents, but common in adults with an prevalence around 1 per 1,000 [1]. Several pediatric case series and retrospective reviews have been reported from different clinical settings including pediatrics, pediatric surgery, and an otorhinolaryngology clinic. The clinical symptoms of hyperparathyroidism at an early stage are mostly nonspecific and atypical, making it very difficult to diagnose. The diagnosis of most cases is delayed and patients may present with complications of long-term hypercalcemia, such as bone deformities or renal nephrocalcinosis. The most common cause of pHP in childhood is parathyroid adenoma, and surgical excision is the most effective treatment. To our knowledge, no previous studies of pHP in the pediatric age group have been conducted in Thailand. In our major tertiary institute in southern Thailand during the past 12 years, we have seen 3 pediatric cases of pHP presenting with different clinical manifestations, and offer these case reports, together with a brief literature review.

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The patients and their parents were informed of this report. Written signed assent from the patients and written signed consent from the parents was provided to report the cases. This retrospective review was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (No. AF/17-03/01.1).

Patient 1

Patient 1 was a 14-year-old Thai girl who presented with progressively worsening bowlegs and lordosis of the spine for 1.5 years. She also had fatigue, decreased appetite, and weight loss. Her height was 135 cm and weight was 29 kg, both below the 3rd percentile for age. A plain X-ray image of both lower extremities revealed diffuse osteopenia, subperiosteal resorption, and genu varus of both knees. Laboratory tests revealed an elevated serum calcium (Ca) level of 14–15 mg/dL (3.50–3.75 mmol/L), a low phosphate (P) level of 1.8 mg/dL, markedly elevated alkaline phosphatase (ALP) at 2,300 U/L, and markedly

elevated parathyroid hormone (PTH) at 1,887 pg/mL. ^{99m}Tc-methoxyisobutylisonitrile (MIBI) revealed hyperfunctioning of her right inferior parathyroid gland, which we suspected as being the result of a parathyroid adenoma. She was initially treated by intravenous hydration, furosemide, and hydrocortisone for 7 days, but her serum Ca was still elevated at 14–15 mg/dL. Intravenous pamidronate 1 mg/kg was administered to attempt to lower the serum Ca, but with minimal effect to 13–14 mg/dL. Surgical excision of the right inferior parathyroid gland was performed on day 10 without any complications during surgery. The pathological report confirmed a parathyroid adenoma. One day postsurgery, she developed severe abdominal pain with distension. Serum amylase and lipase were elevated at 1,880 U/L and 2,850 U/L, respectively, and her serum Ca was 11 mg/dL. An abdominal CT revealed 30% necrosis of the pancreas without calcification and no nephrocalcinosis. Acute pancreatitis was diagnosed. After withholding oral intake of food and fluids, and supportive care for 2 days, her condition improved with serum Ca at 9–10 mg/dL. On the third postoperative day, she developed carpopedal spasms with her serum Ca declined further to 6.5 mg/dL. Despite 10% calcium gluconate 20 mL intravenously every 2–3 hours for 7 days, she still had persistent hypocalcemia with serum Ca at 6–7 mg/dL, and hungry bone syndrome was diagnosed. On days 8–10 postoperation, the hypocalcemia gradually improved with intravenous calcium gluconate 10 mL every 4–6 h, and later on day 14 she could be switched to oral calcium carbonate 2,500 mg/day (elemental calcium 1,000 mg/day) and 1-α-cholecalciferol 1 μg/day with serum Ca 8.5–9.5 mg/dL. She was discharged home on day 24 postsurgery with oral calcium carbonate 2,500 mg/day and 1-α-cholecalciferol 0.5 μg/day, which she continued for 1.5 years. After discontinuation of these medications for 12 months, her serum Ca was 9–10 mg/dL, P 4–5 mg/dL, ALP 300–350 IU/L, and PTH 35–40 pg/mL. Three years later, corrective osteotomy was performed to correct her bowlegs.

Patient 2

Patient 2 was a 15-year-old Thai boy with a history of hip pain and constipation for 3 years. Plain X-ray imaging of the hip revealed a diffuse osteopenia with coarse trabeculation, geographic osteolytic lesions without a sclerotic rim suggestive of brown tumors of the greater trochanter of the right femur and diaphysis of the left femur. His height was 145 cm and weight was 49 kg, both below the 3rd percentile. Initial investigations revealed serum Ca 12 mg/dL (3.00 mmol/L), low serum P 1.3 mg/dL, elevated ALP 3,350 U/L, and markedly elevated PTH 1,185 pg/mL. ^{99m}Tc-MIBI showed hyperfunctioning of the right lower parathyroid gland. Renal ultrasonography revealed normal parenchyma, no nephrocalcinosis, nor renal calculi. After initial hypercalcemia management (intravenous fluid hydration, furosemide, and hydrocortisone) for 2 days and serum Ca 11.5 mg/dL, the boy underwent right inferior parathyroid excision and the pathology found a parathyroid adenoma. One day postsurgery, serum Ca dropped to 6.0 mg/dL and the patient developed carpopedal spasm. Hungry bone syndrome was diagnosed because of persistent hypocalcemia despite treatment with 10% calcium gluconate 20 mL intravenously every 1–2 h with serum Ca 5–6 mg/dL for 12 days. During days 13–20 postoperation, the hypocalcemia gradually improved with 10% calcium gluconate 20 mL intravenously every 3–4 h. Subsequently, he was treated with oral calcium carbonate 2,500 mg/day and 1-α-cholecalciferol 1 μg/day for 1.5 years with serum Ca 8.5–9.5 mg/dL, at which time the treatment was discontinued, with ultimately his serum Ca at 9.0–9.5 mg/dL, P 3.5–4.5 mg/dL, ALP 270–320 U/L and PTH 30–40 pg/mL.

Patient 3

Patient 3 was an obese 11-year-old Thai boy who was referred for evaluation of persistent hypercalcemia. He initially presented at his local hospital with acute abdominal pain, which was diagnosed as acute pancreatitis based on an elevated level of serum amylase of 745 U/L and abdominal ultrasonography, which showed an enlarged pancreas. He had normal serum electrolytes and calcium level. His weight was 71.5 kg and height was 160.5 cm, both of which were over the 97th percentile for his age. His blood pressure was normal at 110/70 mmHg. While withholding oral intake of food and fluids, and providing intravenous fluid treatment for acute pancreatitis for 14 days, he developed polyuria. Laboratory investigations revealed elevated serumCa at 14.1 mg/dL (3.52 mmol/L), P 3.3 mg/dL, ALP 161 U/L, and mildly elevated PTH of 161 pg/mL. A ^{99m}Tc-MIBI scan revealed active uptake by both inferior parathyroid glands suggesting their hyperfunction, indicating possible parathyroid hyperplasia. The patient was checked for adrenal function, pheochromocytoma,

and prolactinoma to exclude multiple endocrine neoplasia (MEN), and all were negative. He was treated with intravenous fluid and furosemide. Surgical excision of both inferior and left upper parathyroid glands was performed after stabilization and serum Ca declined to 11–12 mg/dL. Histopathology found parathyroid hyperplasia. After the surgery, serum Ca returned to a normal range of 9–10 mg/dL and the PTH level was 26–35 pg/mL. No clinical or laboratory hypocalcemia was observed. The patient remained well during the 4-year follow-up without any medication.

Discussion

pHP in the pediatric age group is extremely rare with an estimated prevalence of 2–5 per 100,000, most of which are in the adolescent age group [1]. However, in two large case series, only 30–60 pediatric patients were collected in 20–30 years, and the prevalence was calculated to be even rarer than estimated and around 1 in 250,000 to 300,000 [2, 3]. In our institute, a tertiary care hospital in southern Thailand, only 3 cases have been encountered in 10 years, all in patients 11–15 years of age, like other studies in which most cases were in the adolescent age group [1-9].

The clinical symptoms of early stage hypercalcemia are nonspecific, including anorexia, fatigue, abdominal pain, diarrhea or constipation, and polyuria. In a large case series (**Table 1**), the correct diagnosis was normally delayed for years because most of the patients present with bone symptoms (30%–40%), such as osteopenia, bone pain, fractures, and/or renal involvement (40%–50%), such as nephrocalcinosis or renal calculi, both of which are the complications associated with long term hyperparathyroidism [1-3, 9]. Our patients 1 and 2 presented with bone involvement, which has been noted in a number of other studies [3, 4, 6-8]. Furthermore, a plain X-ray image of the femur of patient 2 revealed an extensive brown tumor caused by a high metabolism of bone and its turnover, which has only infrequently been reported [10, 11]. Interestingly, patient 3 presented with acute pancreatitis, a relatively uncommon presentation recorded in less than 15% of reported cases [1, 5, 12]. Patient 1 developed acute pancreatitis, just one day after surgical excision of a parathyroid adenoma. The pathophysiology of pancreatitis in a primary hyperparathyroid patient might be the result of calcium elevation, leading to pancreatic protease activation, leading then to acute inflammation of the pancreas [13, 14]. Surprisingly, despite a long history of bone involvement as shown by a markedly elevated level of ALP, osteopenia, bowleg, and severe short stature in patients 1 and 2, they had no detectable nephrocalcinosis or nephrolithiasis by abdominal CT imaging in patient 1 or ultrasonography in patient 2. Nephrocalcinosis and nephrolithiasis were common findings in large case series of white patients with European ancestry [2, 5, 9, 12]. The absence of renal involvement in patients 1 and 2 could not be explained. Patient 3 presented with acute pancreatitis in an earlier phase of hypercalcemia, which had a short clinical course, and might not have had bone involvement as ALP was at a normal level. However, a case series of hyperparathyroidism in pediatric patients from Asian countries found a common presentation of bone involvement (70%) and a lower presentation of renal involvement of 40% [6, 8].

All of our patients were given a Tc-MIBI scan to localize the lesion. In other studies, other modalities have been used such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). In earlier studies, ultrasonography played a major role as a diagnostic tool with a sensitivity of 55%–86% and specificity 67%–70% [1, 2, 5]. However, in later studies, MIBI scans have been used, with a higher sensitivity of 90% [7, 8]. One group of investigators recommended that a combination of ultrasonography and MIBI scan could be the evaluation of choice, and that MRI or CT should be preserved for cases of uncertain diagnosis [8]. MIBI scans in our patients 1 and 2 showed hyperfunctioning of the right inferior parathyroid gland suggestive of parathyroid adenoma, while in Patient 3 it showed hyperfunctioning of both inferior parathyroid glands suggestive of parathyroid hyperplasia. The results of MIBI scanning can help in clinical decision making for surgical excision of adenoma or excision of 3 hyperplastic parathyroid glands.

The standard preoperative medical management for primary hyperparathyroidism is to treat the patient for symptomatic hypercalcemia to prepare them for surgery. Our patients were treated aggressively with intravenous fluid combined with diuretics and glucocorticoid, but their calcium level remained high. Therefore, the first patient was treated with bisphosphonate. The effectiveness in calcium normalization by medical treatments in pediatric patients with primary hyperparathyroidism are limited and varied [15].

Table 1. Summary of clinical characteristics of patients with hyperparathyroidism

	No of patients	Age (years)	Male: female ratio	Adenoma (%)	Bone presentation (%)	Renal complication (%)	PTH level (pg/mL)	Serum calcium level (mmol/L)	Acute pancreatitis (%)	Hungry bone syndrome (%)
Lawson et al. (1996) [3]	11	12–17	0.8	100	75	45	79–930	2.64–4.2	NA	NA
Harman et al. (1999) [5]	33	9–19	1.1	94	27	42	27–1,700	2.55–4.55	3	NA
Kollars et al. (2005) [1]	52	4–18	0.67	65	34	33	19–1,700	2.5–4.0	7	NA
Venail et al. (2007) [4]	4	7–14	0.33	100	50	50	87–1,580	2.96–4.34	0	50
Libansky et al. (2008) [12]	10	10–17	1	100	30	50	83–547	2.78–3.64	10	NA
Bhadada et al. (2008) [6]	11	5–18	0.57	91	91	50	128–2,085	2.12–3.40	14	77
Mallet et al. (2008) [2]	44	6–18	0.69	66	16	41	56–2,214	2.5–4.33	NA	NA
George et al. (2010) [7]	18	10–18	0.29	100	89	39	80 ± 66	3.35 ± 0.49	5.5	28
Durkin et al. (2010) [9]	12	10–18	0.09	75	NA	25	77–300	2.73–3.98	0	NA
Li et al. (2012)[8]	12	9–16	0.71	100	92	75	105–2,800	3.25–5	8	NA

PTH, parathyroid hormone; serum calcium level in mg/dL = mmol/L × 4

Adenoma excision was performed in all cases without surgical complications. Two of our patients had a single adenoma, but the third had hyperplasia. In most previous reported cases (69%–100%), primary hyperparathyroidism in children was caused by a single adenoma, with only a few cases of parathyroid hyperplasia [1, 2, 6, 9]. Our Patient 3 who had parathyroid hyperplasia was evaluated using hormone panels for MEN because MEN has been shown to have a high association with parathyroid hyperplasia [3]. The incidence of MEN is relatively low. This patient was followed-up for 4 years without any sign of MEN. However, long term follow-up is needed for early detection of endocrine neoplasia.

The resection of the parathyroid adenoma resulted in symptomatic hypocalcemia in patients 1 and 2. Hungry bone syndrome was diagnosed in these 2 patients and they required intensive intravenous calcium replacement for 14–20 days. Other studies found that transient hypocalcemia is a common complication after surgery, but hungry bone syndrome was reported in only some series [3, 6, 7]. All our patients eventually fully recovered with no recurrence of hyperparathyroidism after 4–12 years of follow-up.

Conclusion

To our knowledge, this is the first case series of primary hyperparathyroidism in a pediatric setting in Thailand. The clinical presentations varied and were nonspecific. We recommend initial laboratory screening in patients with nonspecific symptoms and complaints of persistent bone pain. Appropriate investigations to confirm or eliminate primary hyperparathyroidism should be made, as an early diagnosis can facilitate early treatment and prevent the organ damage that can result from delayed diagnosis.

Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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