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Elevation of Parathyroid Hormone Levels after Surgery in Childhood-onset Primary Hyperparathyroidism : A Case of an 11-year-old Boy

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Primary hyperparathyroidism (PHPT) is rare in children. The endocrinological management after parathyroidectomy in children is not well established. The patient reported here was an 11-year-old boy who underwent parathyroidectomy for PHPT. He started taking calcium lactate hydrate and alfacalcidol 6 days after surgery to prevent postoperative hypocalcemia. His intact parathyroid hormone (PTH) level subsequently increased over the 2 months after surgery, while his serum calcium levels were stable. Although we were concerned about recurrence, his intact PTH level subsequently decreased, and his bone mineral density (BMD) improved postoperatively. Three years after parathyroidectomy, his intact PTH level and BMD are normal, and he is growing normally. It was thought that his transient intact PTH elevation had been caused secondarily by insufficient calcium supplementation after surgery, as suggested by low urine calcium levels at that time. Fortunately, in our case, growth and BMD were not affected postoperatively. Nevertheless, in pediatric cases of PHPT, following up the postoperative endocrinological course is thought to be necessary to obtain healthy growth in terms of stature and bone. *Shinshu Med J 73 : 185—192, 2025*

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Key words : primary hyperparathyroidism, parathyroidectomy, calcium homeostasis

I Introduction

Primary hyperparathyroidism (PHPT) is rare in children, with an estimated incidence of 2 to 5 children in 100,000[1]. PHPT is caused by excess autonomous parathyroid hormone (PTH) secretion in the parathyroid gland. Hyperparathyroidism causes hypercalcemia, which is often asymptomatic or exhibits nonspecific symptoms, but bone disorders such as fractures can occur in such cases due to secondary osteoporosis. For radical treatment of PHPT, excision of the pathological parathyroid gland can be performed. Postoperatively, hypocalcemia can occur due to decreased PTH secretion and rapid calcium influx into the bone, referred to as hungry bone syndrome (HBS). HBS is treated by administering calcium and vitamin D metabolites. Although childhood is a critical period for bone growth, perioperative methods for managing PHPT in childhood to achieve healthy growth are not well established because of its rarity.

PTH elevation with a normal calcium level after successful surgery for PHPT is reported in adult patients, the prevalence of which is 3 %-46 %[2]. Such elevation is considered to occur due to the activity of the remaining parathyroid glands to maintain serum calcium homeostasis, which is related to bone hunger, vitamin D deficiency (defined as 25-hydroxyvitamin D＜10ng/ml), a sudden decrease in calcium levels, or a reduction in renal function[3]. It is sometimes necessary to identify whether PTH elevation after parathyroidectomy reflects a recurrence of PHPT or other disorders of calcium homeostasis.

Herein, we report a pediatric case of PHPT exhibiting transient intact PTH elevation after parathyroid-

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Table 1　Dose of medication

Medication at the local hospital		
medication	**dose**	**dose/weight**
infusion of normal saline	2,400 ml/day	77 ml/kg/day
IV of furosemide	60 mg/day	1.9 mg/kg/day
IDI of elcatonin	40 units/day	1.2 units/kg/day
Medication at our hospital before surgery		
infusion therapy	adjusted targeting urine output over 3 ml/kg/h	
IV of furosemide		
IDI of elcatonin	60 units/day	2.1 units/kg/day
IDI of pamidronate disodium hydrate	30 mg	1.0 mg/kg
Medication at our hospital after surgery		
oral calcium lactate hydrate	3 g/day	0.1g/kg/day
oral alfacalcidol	0.75 μg/day	0.02 μg/kg/day

IV : intravenous injection, IDI : intravenous drip infusion

ectomy, focusing on postoperative 3-year management following a previous report from our hospital[4].

Note that "intact PTH" means measured intact PTH, whereas "PTH" means the hormone secreted by parathyroid glands in this report. However, some reference reports did not clearly distinguish PTH whether measured PTH is intact PTH or not. We described intact PTH or PTH as they were described in those reports.

Ⅱ　Case Presentation

An 11-year-old boy with no medical history was found to have high serum calcium levels during an annual medical check-up at school. His height was 147.0 cm (+0.8 standard deviation (SD)), and his weight was 34.4 kg (−0.3 SD). He had no familial history of hypercalcemia, urinary tract stones, or disease associated with multiple endocrine neoplasia. Six months later, he experienced abdominal pain and nausea. His symptoms lasted for 3 months, during which he lost 3.1 kg ; therefore, he visited a local hospital. The main findings from the local hospital were as follows : albumin-corrected serum calcium level 14.3 mg/dl (normal : 8.7-10.3 mg/dl), ionized calcium level 2.04 mmol/l (normal : 1.13-1.32 mmol/l), serum phosphate level 2.8 mg/dl (normal : 2.5-4.6 mg/dl), intact PTH level 405 pg/ml (normal : 14-79 pg/ml), and urine calcium/creatinine ratio 0.79, while neck ultrasonography revealed a 15×9 mm mass behind the right lobe of his thyroid gland. Based on these results, he was suspected of being PHPT. He was treated with intravenous normal saline, furosemide, and elcatonin for a week **(Table 1)**. However, his hypercalcemia and symptoms did not improve. He was transferred to our hospital for intensive care and surgical treatment.

His height and weight were 150.0 cm (+0.6 SD) and 28.6 kg (−1.2 SD), respectively, on admission to our hospital. The laboratory findings revealed hyperparathyroidism **(Table 2)**. There were no palpable masses on his neck. Contrast-enhanced computed tomography (CT) indicated the right upper parathyroid gland enlargement **(Fig. 1A, B)**, and Tc-99m sestamibi scintigraphy revealed some uptake in the same lesion detected on the CT scan **(Fig. 1C, D)**. The 24-hour urine sample and lumbar (L1-L4) bone mineral density (BMD) were not assessed preoperatively because prompt depression of serum calcium and preoperative general care were needed. In addition to adequate infusion therapy and continued diuretic administration, the dose of elcatonin was increased, and

Table 2 Laboratory findings on admission to our hospital

Blood (normal range)			1,25(OH)D (20–70)	113	pg/ml	**Urine**		
Alb (4.1–5.1)	4.1	g/dl	25(OH)D (>20)	25.5	ng/ml	Ca/Cr	1.7	
BUN (6.6–19.6)	12.1	mg/dl	intact PTH (10–65)	406.3	pg/ml	iP/Cr	0.8	
Cre (0.35–0.58)	0.82	mg/dl	PTH-related peptide	<1.0	pmol/l	%TRP	60.3	%
ALP (154–431)	325	U/l(IFCC)	calcitonin (<9.52)	3.38	pg/ml			
Na (137–144)	150	mEq/l	prolactin (3.6–16.3)	2.0	ng/ml			
K (3.6–4.7)	3.0	mEq/l	growth hormone	0.2	ng/ml			
Cl (101–110)	114	mEq/l	ACTH (7.2–63.3)	43.4	pg/ml			
Ca (8.7–10.2)	17.7	mg/dl	cortisol (5.0–15.5)	45.7	μg/dl			
Ca^{2+}	9.3	mg/dl	gastrin (37–172)	168	pg/ml			
iP (3.9–5.8)	1.6	mg/dl	IRI (5–25)	9.4	μU/ml			
Mg (1.8–2.3)	1.4	mg/dl	catecholamines	normal				
Glu (60–110)	134	mg/dl	glucagon, serum and urine C-peptide, and 24-hour urine sample				NM	

NM : not measured

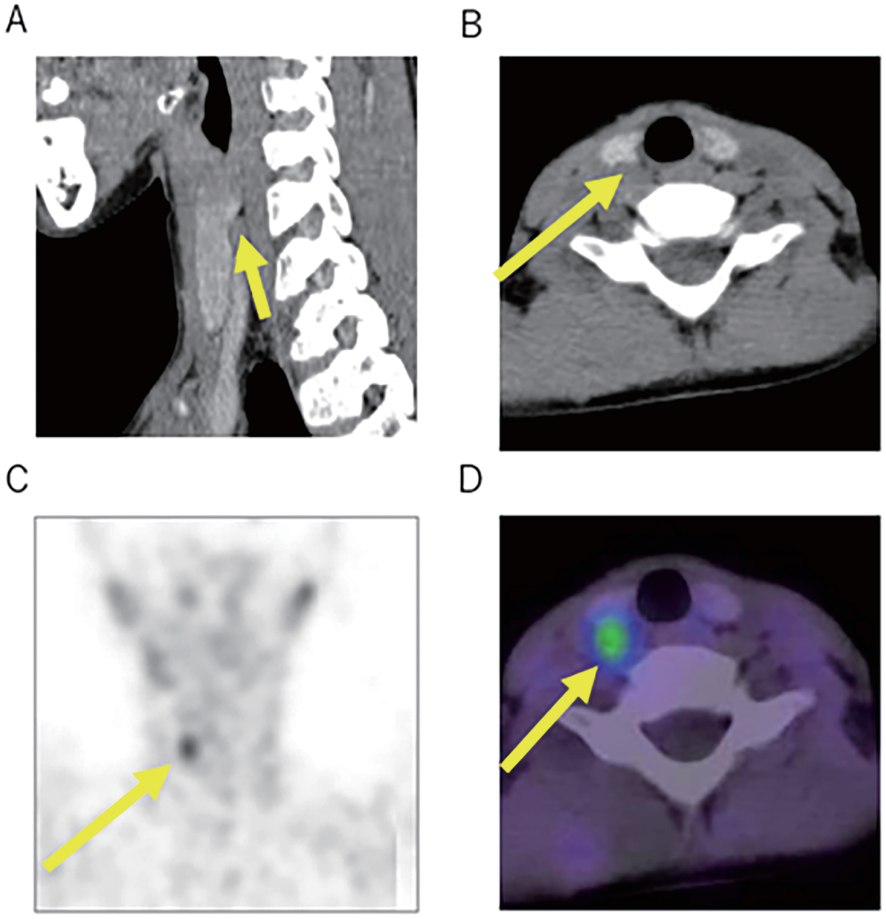

Fig. 1 Radiological findings. Contrast computed tomography (A, B) and Tc-99m sestamibi scintigraphy (C, D). Arrows indicate an enlarged right superior parathyroid gland.

pamidronate disodium hydrate was administered for severe hypercalcemia **(Table 1, Fig. 2)**. Because the patient was unresponsive to medical therapy, parathyroidectomy was performed three days after admission to our hospital.

The enlarged right upper parathyroid gland was successfully removed. Pathological examination of the resected tissue revealed parathyroid adenoma. DNA

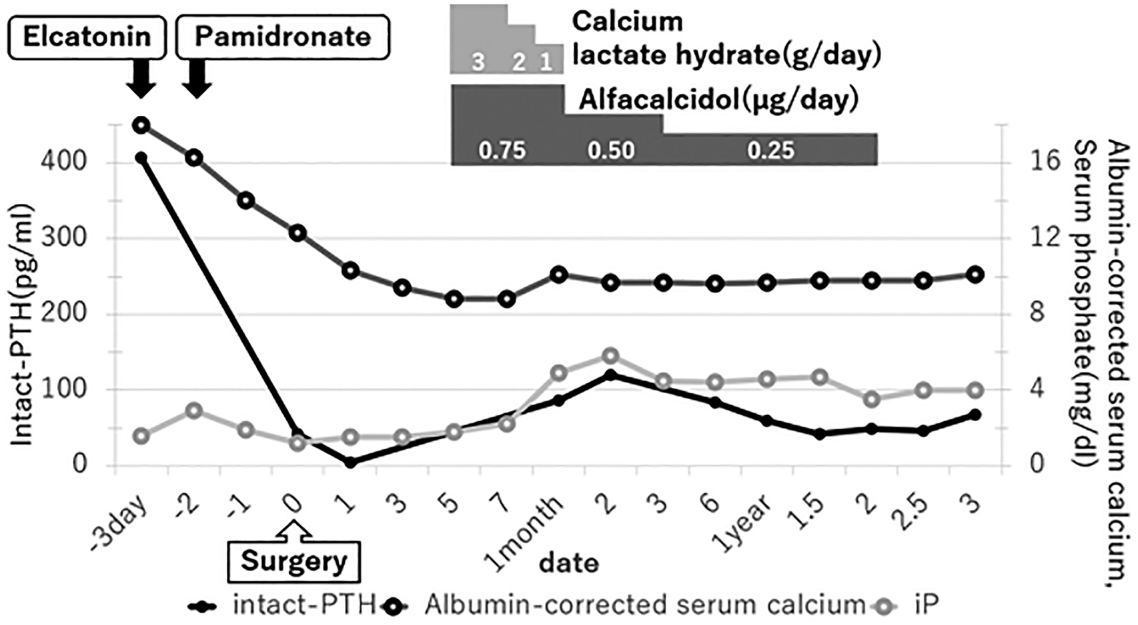

Fig. 2 Albumin-corrected serum calcium (mg/dl), serum phosphate (mg/dl), and intact PTH (pg/ml) concentrations before and after surgery.

sequencing and multiplex ligation-dependent probe amplification with blood samples detected none of the pathological variants related to familial PHPT (*MEN1*, *CDKN1B*, *RET*, *CDC73*, *CASR*, *GNA11*, *AP2S1*, or *GCM2*).

The patient's postoperative serological course is summarized in **Fig. 2**. His intact PTH level dropped to 41.7 pg/ml (normal : 10-65 pg/ml) in the intraoperative test performed 15 min after the tumor resection and to 5.1 pg/ml the following day. His lumbar (L1-L4) BMD result was 0.682 g/cm^2 (Z score : −0.7 SD) on day 5. Calcium lactate hydrate and alfacalcidol **(Table 1)** were initiated to prevent hypocalcemia. The albumin-corrected serum calcium level at discharge was 8.8 mg/dl (normal : 8.7-10.2 mg/dl), and the serum phosphate level was 2.2 mg/dl (normal : 3.9-5.8 mg/dl).

The oral medications were gradually reduced according to the serum calcium and phosphate levels. The calcium lactate hydrate was discontinued 1 month after surgery because the serum calcium was in the normal range. His serum calcium, phosphate, ALP, and creatinine levels were normal 2 months after surgery, but the intact PTH level increased to 120.6 pg/ml. His ionized calcium level was 4.9 mg/dl, 25-hydroxyvitamin D was 21.5 ng/ml (normal : >20.0 ng/ml), and the urine calcium/creatinine ratio was 0. Neck ultrasonography did not show any parathyroid gland enlargement. Alfacalcidol supplementation was performed until the intact PTH level decreased to within the normal range and remained there. The patient's lumbar (L1-L4) BMD was 0.774 g/cm^2 (+0.1 SD) 6 months after surgery and 0.904 g/cm^2 (0 SD) 2 years after surgery. At the time of writing, 3 years have passed since he underwent parathyroidectomy. His height and weight are 177.2 cm (+1.8 SD) and 47 kg (−1.8 SD), respectively, at 14 years and 7 months old **(Fig. 3)**, while his intact PTH, serum calcium, and phosphate levels are 67.3 pg/ml, 9.8 mg/dl, and 4.0 mg/dl, respectively. He has no symptoms.

Ⅲ Discussion

An 11-year-old boy underwent parathyroidectomy for PHPT and his intact PTH level decreased after parathyroidectomy. However, intact PTH rose again 2 months after surgery with normal serum calcium level. In children, HBS is one of the common complications of parathyroidectomy for the treatment of PHPT. HBS is characterized by severe and prolonged hypocalcemia due to decreased PTH secretion after parathyroidectomy. On the other hand, there is no

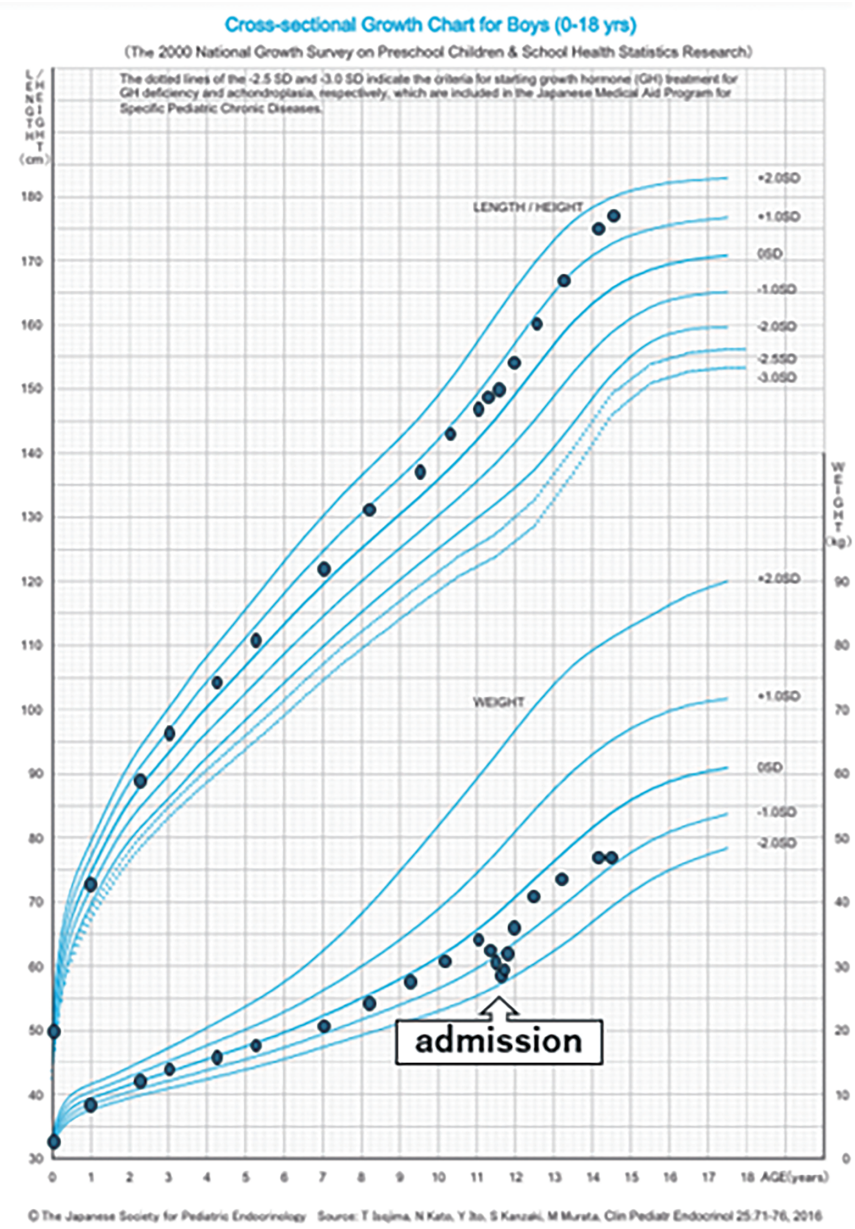

Fig. 3　Growth chart from birth to 3 years after surgery.

report about postoperative PTH elevation keeping serum calcium levels in pediatric cases.

It is reported that rebound PTH elevation after curative parathyroidectomy is not rare in adult patients[2)3)5)]. It is defined in cases whose PTH levels elevate with normal or low calcium at least once within 6 months postoperatively and later drop back to within the normal range. PTH secretion after parathyroidectomy in the remaining parathyroid glands is thought to occur due to disordered calcium homeostasis. After parathyroidectomy, temporary hypocalcemia could occur due to hypoparathyroidism. Then, the remaining parathyroid glands increase PTH secretion to maintain serum calcium levels. The laboratory factors related to this condition are multifactorial and controversial. It is suggested that 25-hydroxyvitamin D is lower (median : 11.8 ng/ml) and PTH is higher (median : 212.4 pg/ml, normal range : 15-65 pg/ml) preoperatively in cases with elevated PTH after parathyroidectomy[3)]. In our case, while the preoperative 25-hydroxyvitamin D level was not critically low, the preoperative intact PTH level was significantly higher than the preoper-

ative data reported by Lee et al.[3]. We should have recognized the risk of postoperative PTH elevation reflecting a disorder of calcium homeostasis.

Recurrent hyperparathyroidism was also a concern in this context. It has been reported that such recurrence may first be predicted by high intact PTH levels, followed by the onset of hypercalcemia[6]. Eventually, we concluded that the current patient had not relapsed because the hypercalcemia that was expected to ensue did not occur, and intact PTH levels then gradually decreased. It was also useful to assess BMD because it typically increases after successful parathyroidectomy in adult patients[7][8]. In childhood, bone mass is acquired in the balance of various factors such as growth rate, pubertal changes, and lifestyle[9]. Our case followed the process of a boy's typical growth in height, so his BMD was expected to increase in the growth process. The improvement of BMD Z-score matched with age and sex in the postoperative course indicated no obvious impairment suggesting recurrence in acquiring bone mass. Morimoto *et al.* reported that a pediatric patient with PHPT experienced a decrement in BMD after parathyroidectomy[10]. In this case, vitamin D deficiency was pointed out after surgery. When PTH elevation after parathyroidectomy occurs, continuous careful assessment of serological and radiological findings is needed to differentiate recurrence or other factors.

Besides recurrence, familial hypocalciuric hypercalcemia (FHH) should be differentiated because parathyroidectomy does not cure the disease. FHH is a genetic condition caused by inactivation mutations in the calcium-sensing receptor gene. FHH is typically inherited as an autosomal dominant pattern. Usually, hypercalcemia and hyperparathyroidism are mild, and serum magnesium levels elevate in FHH compared to PHPT. All parathyroid glands would be enlarged in cases with FHH. Low urinary calcium (<200 mg/24 hours) despite hypercalcemia and low calcium clearance to creatinine clearance ratio (Ca/Cre ratio <0.01) is used to differentiate FHH from PHPT[11][12]. We considered it appropriate to diagnose our case with PHPT in terms of no familial history of hypercalcemia, the obvious elevation of serum calcium and intact PTH on admission, low serum magnesium, the presence of only an enlarged parathyroid gland, and spot urine Ca/Cre>0.01 before medication. The 24-hour urine sample may be useful in clearer differentiation, although we did not measure it to promptly cope with the general condition's deterioration due to hypercalcemia. Consequently, none of the mutations associated with FHH (*CASR*, *GNA11*, and *AP2S1*) were detected.

Administration of bisphosphonate before surgery is one of the factors that could affect bone metabolism after surgery. Kota SK et al. excluded patients taking medication known to interfere with calcium or vitamin D metabolism for at least 3 weeks before surgery[5], while other reports did not mention the use of bisphosphonates. Tanaka *et al.* reported no significant difference was noted in the perioperative bisphosphonate medication between patients whose PTH was elevated after parathyroidectomy and the others[13]. In addition, it is reported serum calcium will reach nadir at 2-4 days after intravenous bisphosphonate[14]. Therefore, we considered that the impact of bisphosphonate on intact PTH elevation 2 months after surgery in our case was low.

Looking back to the postoperative course in our case, urinary calcium level was low 2 months after surgery when intact PTH peaked. At this time, serum calcium, phosphate, 25-hydroxyvitamin D, and renal function were not impaired. These findings indicated the possibility of potential calcium deficiency compensated by PTH elevation. Kota SK et al. reported that calcium supplementation in the first 6 months after parathyroidectomy was associated with a lower incidence of PTH elevation[5]. We should have considered continuous and adequate postoperative supplementation with calcium lactate hydrate for at least 6 months. Appropriate administration methods of calcium supplementation for child cases are challenges for the future. We should have measured bone turnover markers to assess bone metabolism more thoroughly after parathyroidectomy.

Fortunately, the patient's postoperative growth and BMD reflected normal development. However, since childhood is a critical period for accelerations in growth

and BMD acquisition, it is appropriate to continue medical management by following up on endocrinological findings such as growth, BMD, and markers involved in calcium homeostasis (e.g., serum PTH, calcium, phosphate, ALP, vitamin D, urine calcium, and bone turnover markers) until the sufficient recovery and calcium replenishment are achieved. The long-term effect of rebound PTH after parathyroidectomy in children is a topic for future study.

This case also suggested the importance of physical examinations in schools. This patient did not recognize the need for a medical consultation when hypercalcemia was identified at school because he was initially asymptomatic. It is important to inform pupils and their parents of the importance of medical check-ups for the early detection of diseases, even if they are asymptomatic.

Ⅳ Conclusion

We experienced a child's case presenting rebound intact PTH levels after parathyroidectomy for PHPT with normal serum calcium level. In adult cases, this condition is thought to be caused by disordered calcium homeostasis. Various parameters, such as PTH levels, vitamin D, renal function, urine calcium secretion, BMD, and medication control calcium homeostasis. Recurrence of tumors and other differential diagnoses should also be excluded. We considered that potential calcium deficiency caused by inadequate calcium supplementation was one of the reasons for postoperative intact PTH elevation. Clarifying more detailed mechanisms and long-term effects on bone metabolism in child cases is a future issue. We should comprehensively assess bone metabolism and the necessity of intervention for potential postoperative calcium deficiency for the patients of PHPT, especially in pediatric cases, to ensure subsequent healthy growth and maintain calcium homeostasis.

Conflict of interest statement : The authors declare no conflicts of interest.

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Ethical considerations : Written informed consent was obtained from the patient and his parents to publish this case report and accompanying images.

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