Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.22180

Clinical Profile of Parathyroid Adenoma in Children and Adolescents: A Single-Center Experience

Sirmen Kızılcan Çetin, Zeynep Şıklar, Zehra Aycan, Elif Özsu, Ayşegül Ceran, Seda Erisen Karaca, Gizem Senyazar, Merih Berberoğlu

Department of Pediatric Endocrinology, Ankara University, School of Medicine, Ankara, Turkey

What is already known on this topic?

- *Pediatric cases have a wide range of nonspecific features, and most pediatric case series include patients >18 years of age.*
- *There is not much experience with the characteristics of parathyroid adenoma in childhood.*

What does this study add on this topic?

- *Parathyroid adenoma (PTA) should be considered in children with hypercalcemia after the first decade.*
- *Suspected cases should undergo both ultrasonography and scintigraphy to detect PTA.*

ABSTRACT

Objective: Parathyroid adenoma is less common than in adulthood, but its morbidity is higher in children. We aimed to evaluate the clinical characteristics of parathyroid adenoma and our clinical experience since the early disease is often asymptomatic and late diagnosed.

Materials and Methods: From 2010 to 2020, all children diagnosed with parathyroid adenoma at our institution were reviewed. We evaluated clinical, biochemical, and radiological aspects and follow-up characteristics.

Results: Eight subjects (F/M = 6/2) ranged in age from 10 to 17 years. Three were symptomatic. The symptoms and findings were stomachache (n = 3), myalgia (n = 2), weakness (n = 2), pancreatitis (n = 1), constipation (n = 1), nausea (n = 1), bone ache (n = 1), and anorexia (n = 1). Laboratory findings on admission were as follows: the mean calcium was 12.59 ± 1.28 (11.2-15.3) mg/dL and the mean parathyroid hormone was 244.81 ± 173.61 (74.9-645.4) pg/mL. The most common localization was the lower part of the left parathyroid gland. Parathyroid adenoma could not be demonstrated by ultrasonography in 2 patients. Tc-99m-Sestamibi scintigraphy revealed the presence of parathyroid adenoma in only 7 of 8 patients. All underwent parathyroidectomy. In our follow-up, 2 subjects needed reoperation. A molecular analysis of 6 cases could be done. One was *MEN1* positive. *RET* sequence analysis of 2, and *Casr*, *GNA11*, and *AP2S1* sequence analysis of 3 were normal.

Conclusion: Parathyroid adenoma should be considered in children older than the first decade with hypercalcemia. Suspected cases should undergo both ultrasonography and scintigraphy. Early diagnosis prevents the patients from serious complications of hypercalcemia such as nephrocalcinosis, diabetes insipid, and arrhythmia. It is significant to perform surgery in centers experienced in parathyroidectomy to minimize postoperative complications.

Keywords: Hypercalcemia, parathyroid adenoma, primary hyperparathyroidism, parathyroid imaging, parathyroid

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a rare, complex endocrine disorder caused by autonomic increased activity of the parathyroid gland.[1,2] It may occur incidentally as asymptomatic hypercalcemia. Although it is common in adults, it is rare in children and adolescents. The prevalence of pediatric PHPT is 2-5/100 000. Sporadic parathyroid adenomas (PTA) are the most common (80%) cause of PHPT.[1-3] The female-to-male ratio of PHPT is approximately 3-4 : 1.[3]

It shows bimodal age distribution with an early peak in the neonatal period and a second peak from 6 years of age to adolescence. Primary hyperparathyroidism is typically due to a calcium-sensing receptor (*CaSR*) mutation. Primary hyperparathyroidism in children

Corresponding author:
Sirmen Kızılcan Çetin
✉ drsrmnkzlcn@gmail.com
Received: July 8, 2022
Accepted: October 16, 2022
Publication Date: December 29, 2022

Cite this article as: Çetin SK, Şıklar Z, Aycan Z, et al. Clinical profile of parathyroid adenoma in children and adolescents: A single-center experience. *Turk Arch Pediatr.* 2023;58(1):56-61.

and adolescents is most commonly caused by a single PTA (70%-80%). Multiglandular disease and multiple adenomas are less seen (approximately 15%-20%).[4-6] Adenomas are mostly sporadic. It may be a manifestation of multiple endocrine neoplasias (MEN) syndromes such as MEN1 and MEN2A or familial isolated hyperparathyroidism syndromes such as hyperparathyroidism jaw tumor syndrome and X-linked hypophosphatemia.[1,2,5]

Symptoms of hyperparathyroidism are constipation, bone pain, fatigue, and depression. Severe hypercalcemia can cause fatal arrhythmias such as short QT(The time from Q wave of QRS complex to the end of the T), ventricular tachycardia, and even ventricular fibrillation. Nephrolithiasis, osteoporosis, bone fractures, osteopenia, pancreatitis, peptic ulcer disease, and hypertension can be observed.[2,4] Symptomatic disease is more common in children with PHPT than in adults (79%-90%), and 44% of organ involvement (e.g., nephrolithiasis, nephrocalcinosis, and bone involvement) can be definitively treated with surgery.[4] Pediatric case reports have a wide range of nonspecific features.

The critical biochemical features of PHPT are a high or inappropriately normal level of serum parathyroid hormone (PTH) in the context of high-normal or elevated serum calcium (Ca) concentration. Familial hypocalciuric hypercalcemia (FHH) and neonatal severe hyperparathyroidism (NSHPT) are characterized by very low urinary Ca excretion (fractional excretion of Ca (FeCa)) less than 1%. In contrast, other forms of PHPT usually have higher urinary Ca levels (FeCa more than 1%).[2]

Germline/somatic mutations or de novo mutations have been identified in the molecular etiology of PHPT. Germline mutations in the *MENIN* (MEN1, OMIM 613733), *RET* (MEN2, OMIM 164761), and *CDKN1B* (MEN4, OMIM 600778) genes lead to multigland hyperplasia. Single PTA is often associated with a somatic mutation in *MENIN* or *PTA1*. Germline or somatic mutations in *HPRT2* (CDC 73) also predispose to familial PTA (OMIM 607391) or carcinoma.[2,7]

If PTA is localized by imaging, then patients with PHPT undergo a parathyroidectomy operation. Biochemical features and clinical findings such as nephrolithiasis, bone fractures, and osteoporosis are improved after surgery.[3]

In the literature, most pediatric case series included patients >18 years of age.[5,8-11] There is not much experience with the characteristics of PTA in the childhood age group. A patient with the asymptomatic disease might have target organ involvement and skeletal or renal involvement. Since most children with PTA are asymptomatic, a thorough evaluation is significant. Early diagnosis prevents morbidity. In this study, we aimed to evaluate the clinical characteristics of PTA and our clinical experience since the early disease is often asymptomatic. We reviewed our experience with PHPT to characterize these children better.

MATERIALS AND METHODS

Study Population

This retrospective case series includes all patients who were diagnosed with PTA at our institution between 2000 and 2021. The ethical committee of Ankara University approved this study (approval number: I1-81-21, 05.02.2021).

Inclusion and Exclusion Criteria

All patients (aged less than 18 years) with PTA were included in the study. Subjects with secondary or tertiary PTA were excluded.

In all children, diagnosis of PTA was based on clinical, biochemical, and radiological evaluation in subjects whose serum PTH was not suppressed despite hypercalcemia.

Data

We collected data from the archive records of the patients. Demographic information, family history, complaints at presentation, anthropometry and physical examination findings in diagnosis and follow-up, laboratory evaluations, systemic disease screening results, and responses to medical and surgical treatments were collected for each subject. At each visit, patients underwent a comprehensive clinical examination.

Anthropometric data such as weight standard deviation (SD), height SD score, and body mass index were derived from retrospective records. Height Z-scores were calculated with the online calculator with reference to the Turkish population.[12,13]

Subjects were followed up regularly every 3-6 months. Serum Ca, phosphate, alkaline phosphatase, parathyroid hormone, 25-OH vitamin D levels, and urine Ca levels were checked according to standard laboratory methods. Preoperative and postoperative biochemical findings were assessed.

The preoperative location of parathyroid abnormalities was evaluated by neck ultrasonography (US) and Tc-99m-Sestamibi scintigraphy. The postoperative pathological evaluation was done for all. If the molecular analysis was studied, the results were evaluated.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences, version 21.0 (IBM Corp., Armonk, NY, USA) was performed. Descriptive analyses were expressed as the mean ± SD, median (minimum; maximum).

RESULTS

Admission Characteristics

In this case series, we report the clinical features of 8 patients (2 males/6 females, mean age 13.8 years, range 10-17 years). The age distribution of all is shown in Figure 1. Two were prepubertal. Only 3 were symptomatic. The symptoms were myalgia (n = 3), fatigue (n = 3), stomachache (n = 2), constipation (n = 1), arthralgia (n = 1), nausea (n = 1), and loss of appetite (n = 1).

The longest symptom among our cases was abdominal pain in case 4. He had been followed up with the misdiagnosis of familial Mediterranean fever at another hospital. He was on colchicine. At admission, his laboratory assessment showed elevated amylase, lipase, hypercalcemia (15 mg/dL), and elevated PTH (645 pg/mL). He had pancreatitis due to hypercalcemia. His serum amylase and lipase levels were decreased. We initiated pamidronate and stopped colchicine. We ruled out

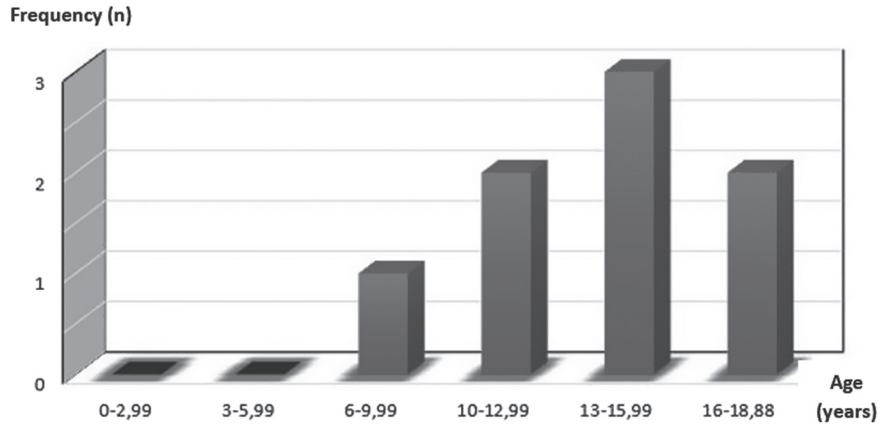

Figure 1. Age distribution of all cases respectively (year).

Brown tumor in his radiological evaluation. On follow-up, he had no complications.

All symptoms and conditions are shown in Figure 2. Three of the cases were diagnosed with incidental hypercalcemia. One had a family history of MEN1 syndrome, and 2 were sisters with a family history of PTA. Case 8 had had worsening headaches over a year and bitemporal hemianopsia. Cranial magnetic resonance imaging revealed a pituitary macroadenoma (12 × 10 × 9 mm) with compression of the optic chiasm and extension to the sella. Prolactin levels had been 118 ng/mL. Except for prolactin, all anterior pituitary functions had been normal. The patient had undergone subtotal transsphenoidal resection. She had been on 0.25-mg oral cabergoline once a week for her residual prolactinoma and daily L-thyroxin therapy due to iatrogenic central hypothyroidism. Her pathological evaluation had been consistent with prolactinoma. She had been followed up at another hospital. She applied to our clinic with incidental hypercalcemia after a year of operation. Combined with the history of pituitary prolactinoma suspected PTA and family history, these findings suggested MEN1 syndrome. Her molecular analysis showed c.1594 C>T (p.Arg532*) mutation in the *MEN1* gene. She is still on close follow-up due to MEN1 syndrome with no complaints.

Laboratory findings on admission were as follows: the mean Ca was 12.59 ± 1.28 (11.2-15.3) mg/dL, the mean phosphorus (P) was 3.58 ± 0.79 (2-4.6) mg/dL, the mean alkaline phosphatase (ALP) was 222.38 ± 116.24 (83-399) IU/L, and the mean PTH was 244.81 ± 173.61 (74.9-645.4) pg/mL, as shown in Table 1.

All subjects underwent neck US. Parathyroid adenoma could not be demonstrated by the US in 2 patients. Tc-99m-Sestamibi scintigraphy revealed the presence of PTA in 7. The most common localization was the lower part of the left parathyroid gland except in 2 cases (Table 2).

The molecular analysis of 6 subjects could be analyzed. One had a family history of MEN1 syndrome, and 2 were sisters with a family history of PTA. Only 1 had *MEN1* [c.1594 C>T

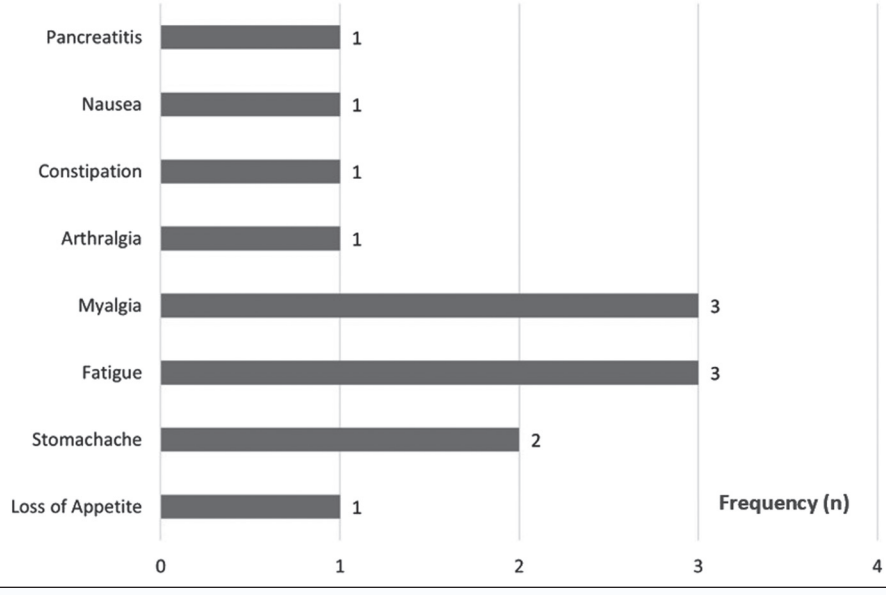

Figure 2. Presenting clinical symptoms and conditions in all cases.

Table 1. Biochemical Characteristics of All Cases

	At Admission	On Operation Day	First Day After Surgery	First Year After Surgery
Ca (mg/dL)	12.59 ± 1.28 12.25 (11.2; 15.3)	11.44 ± 0.94 11.7 (9.6; 12.8)	8.78 ± 0.46 9.03 (8.2; 9.2)	9.72 ± 0.27 9.75 (9.4; 10.2)
P (mg/dL)	3.58 ± 0.79 3.64 (2; 4.6)	3.45 ± 0.61 3.22 (2.5; 4.49)	3.63 ± 0.74 3.59 (2.32; 5.2)	4.63 ± 0.75 4.38 (3.8; 5.94)
ALP (mg/dL)	222.38 ± 116.24 188 (83; 399)	203.25 ± 108.03 191 (76; 363)	195.5 ± 106.07 185.5 (57; 360)	163.33 ± 110.41 122 (53; 362)
PTH (pg/mL)	244.81 ± 173.61 181.1 (74.9; 645.4)	199.21 ± 89.29 211.05 (62; 332.3)	56.94 ± 55.99 40.65 (7.7; 195.9)	44.53 ± 15.31 37.55 (33; 76)
25-OHD (ng/mL)	29.28 ± 3.97 30.17 (22; 34)	-	-	30.24 ± 5.11 30 (22.6; 38)

ALP, alkaline phosphatase; Ca, calcium; 25-OHD, 25-hydroxyvitamin D; P, phosphorous; PTH, parathyroid hormone.

(p.Arg532*)] positive. *RET* sequence analysis of 2, and *Casr*, *GNA11*, and *AP2S1* sequence analysis of 3 were normal.

Treatment and Follow-Up Characteristics

All underwent parathyroidectomy. One subject was on pamidronate, and 1 subject was on alendronate before surgery. The mean Ca decreased to 8.78 ± 0.46 (8.2 -9.2) mg/dL, and the mean PTH decreased to 56.9 ± 55.99 (7.7-195.9) pg/mL on the first postoperative day. After a year of surgery, physical examinations of all were normal, laboratory findings were as follows: the mean Ca was 9.72 ± 0.27 (9.4-10.2) mg/dL, the mean P was 4.63 ± 0.75 (3.8-5.94) mg/dL, PTH was 44.53 ± 15.31 (33-76) pg/mL, as shown in Table 1. The tumor size was 13.80 ± 2.81 mm, ranging from 11 to 19 mm on pathological examination (Table 2).

In follow-up, 2 subjects (cases 5 and 6) needed reoperation. Case 5 was a 10-year-old girl. She had applied due to incidental hypercalcemia with no complaints of hypercalcemia. Laboratory data on admission were as follows: Ca: 12.2 mg/dL, P: 3.7 mg/dL, PTH: 186 pg/mL, ALP: alkaline 399 U/L. Her urinary had increased Ca extraction. The US of the neck showed a hypoechoic, regular lesion, measuring 11 × 5 mm^2. Tc-99m-Sestamibi scintigraphy revealed PTA. She underwent a parathyroidectomy in a week. Parathyroid adenoma was pathologically confirmed. After surgery, her serum PTH was still high (195.9 pg/mL), and her serum Ca level was high (12.8 mg/dL).

We followed her up close. She was on alendronate therapy and had the second reoperation after a month. The surgeons excised the residue tissue of PTA. After surgery, her follow-up Ca and PTH levels were normalized. The molecular analysis of *MEN1* was normal. No signs or symptoms were observed during her follow-up. Case 6, a 13.6-year-old boy, was applied to our outpatient unit. He had had the first symptoms of hyperparathyroidism that appeared 2 months ago, with myalgia,

Table 2. Characteristics of All Cases

Patient	Age/ Sex	Symptoms/Conditions	Family History	Scintigraphy/ Ultrasonography	Pathology	Pathology (Tumor Size)	Localization on Parathyroid	Surgery/ Bisphosphonate	Molecular Analysis	Outcome	Follow-Up (Months)
Case 1	12.12/F	Fatigue, myalgia, arthralgia, constipation, metatarsal fracture	-	+/+	PTA	14 mm	Upper left lobe	+/–	*MEN1*: N	Well	17.23
Case 2	17.44/F	None (incidental hypercalcemia)	Uncle had PTA and Brown tumor	+/–	PTA	13 mm	Lower left lobe	+/–	*MEN1, RET 1, CaSR*: N	Well	38.5
Case 3	14.59/F	None (incidental hypercalcemia)	Sister of case 2	+/–	PTA	14 mm	Lower left lobe	+/–	*MEN1, RET 1, CaSR*: N	Well	11.73
Case 4	9.98/M	Loss of appetite, fatigue, myalgia, nausea, stomachache/pancreatitis	-	+/+	PTA	13 mm	Upper left lobe	+/pamidronate	*MEN1*: N	Well	54.5
Case 5	10.07/F	None (incidental hypercalcemia)	-	+/+	PTA	11 mm	Lower left lobe	+/–	-	Well	2.33
Case 6	13.04/M	Myalgia, fatigue, constipation	-	+/+	PTA	13mm	Right left lobe	+/alendronate	-	Well	34
Case 7	17.57/F	Stomachache	-	+/+	PTA	19 mm	Lower left lobe	+/–	*MEN1, RET, Casr, GNA11, AP2S1*: N	Well	11.4
Case 8	15.60/F	Fatigue, myalgia/ prolactinoma	Cousin had hypercalcemia	–/+	PTA	12 mm	Lower left lobe	+/–	c.1594 C>T (p.Arg532*) in *MEN1*	Well	4.6

PTA, parathyroid adenoma.

fatigue, and constipation. He had had a parathyroidectomy at another hospital. He was referred to our outpatient unit with suspected PTA due to hypercalcemia in his test results. He had no symptoms. His physical examination was normal. His neck US and confirmed suspected PTA at the same spot. Surgeons extracted residual tissue. The histopathological assessment showed a hypoechoic nodular lesion with PTA. After the operation, Ca and PTH were normalized. He had no symptoms on follow-up.

All were followed closely in the postoperative period, and prophylactic Ca replacement and calcitriol treatment were given. Prophylactic treatments were tapered off within close lab evaluation. In the postoperative period, serum and urinary Ca values were closely monitored in the first month and monthly in the first year after discharge. Annual renal ultrasonography (USG) was observed in the follow-up.

All subjects were followed up during 13.80 ± 2.81 (2.33-54) months. Arrhythmia, nephrolithiasis, and bone resorption were not observed in any of the cases. None of them had a Brown tumor.

DISCUSSION

Parathyroid adenoma is very rare in childhood and adolescence.[1-3] Primary hyperparathyroidism is usually caused by a single benign PTA (90%) or rarely multiple adenomas (2%-4%). Parathyroid carcinoma (less than 1%) is extremely rare.[2] Age intervals of PTA were reported in childhood as 7-4 years[14]/9-19 years old.[15] It was similar to our report. In our case series, it is noteworthy that the number of cases between the ages of 13 and 16 is higher. Fewer cases were between the ages of 6 and 9. Similar to the case series in the literature, PTA was more common in girls than boys in our report.[9,10,15,16]

Rampp et al[5] conducted the largest known cohort of adolescents with PHPT in the literature. The most common pathology in this series was single PTA (71%), followed by multiglandular parathyroid disease (23%), double adenoma (2%), and parathyromatosis (1%). Kollars et al[9] defined the pathologies of patients with PHPT as PTA (n = 36), MEN1 (n = 10), MEN2A (n = 3), and familial non-MEN HPT (n = 3). Hsu et al[11] showed PTA in 12 of 17 patients with PHPT. As in our study, these studies proved that PTA is the most common pathology in patients with PHPT. They should be evaluated with further investigations. Sharanappa et al[16] showed that the cure rate after primary surgery was 97%. Our all cases were cured after surgery. Although Kollars et al[9] showed that adenoma was most commonly located superiorly, in our study the most common localization was the lower part of the left parathyroid gland. Ethnicity differences might have caused this situation.

Rapaport et al[17] reported that the duration of symptoms in patients with PTA was quite high, ranging from 2 to 12 years (mean 4.7). Polyuria and polydipsia, the well-known hypercalcemia symptoms, were the most common findings.[17] It has been reported that the diagnosis of PTA is delayed between 2 and 5 years.[9,17] The obscurity, diversity, and confusion of symptoms and signs with other disease symptoms cause a delay in diagnosis. The most common symptom we observed was myalgia and fatigue. Pancreatitis was rarely reported, with a rate of 11.4% of PTA in the literature.[16] The longest symptom among our cases was abdominal pain in case 4 presented with pancreatitis.

Harman et al[15] evaluated 31 cases with PTA. Of these cases, 94% were symptomatic, 42% showed nephrolithiasis, and 27% had bone involvement. Adenoma was detected in 31 cases.[15] Venail et al[14] reported on 4 children with clinical signs of chronic hypercalcemia. Contrary to the literature, polyuria was most frequently observed in this case series.[14] In our case series, we did not have a patient with polyuria. This is because most cases are early diagnosed with subtle findings and coincidental laboratory hypercalcemia. Immediate treatment might have also prevented sufficient time for these findings to develop.

Mallet[18] highlighted that the use of molecular biology tests may be beneficial not only in neonatal cases (*CaSR* mutation) but also preoperatively (*MEN* mutation) in children.[18] In our study, as a result of genetic evaluation, we diagnosed MEN1 syndrome in case 8. She had been diagnosed with prolactinoma.

Primary hyperparathyroidism detected in childhood is more aggressive.[2] For this reason, it is essential to evaluate serum Ca levels in controls to identify patients before they develop symptoms in childhood. The majority of our cases were diagnosed with incidental hypercalcemia.

The first-line methods of imaging the parathyroid glands are ultrasound and/or 99m Tc sestamibi scintigraphy. Parathyroid adenoma is hypoechoic on ultrasound.[4] The US had 60%-93% sensitivity but high specificity (98%) for PTA. Tc-99m-Sestamibi scintigraphy has 92% sensitivity and 97% specificity for PRAD.[5] Excision of the abnormal parathyroid glands is the best treatment for most children diagnosed with PHPT.[5] Among our cases, the US could not detect PTA in 2. Scintigraphy could not identify PRAD in 1.[14]

Minimally invasive parathyroid (MIP) surgery can be performed on patients who have well-identified single PTA. Intraoperative measurement of PTH levels ensures successful parathyroidectomy with MIP surgery.[2] Postoperative pain complaints are less after MIP surgery. Hospitalization time is shorter and provides better cosmetic results.[5] Although this method was not used in the surgery of our cases, this method should be considered by surgeons among the surgical options. In most pediatric and adult patients with PHPT, surgery is curative. There are cases with FHD as a tiny group for whom surgical treatment does not show any benefit. Therefore, it is essential to exclude this diagnosis in order to prevent unnecessary operations on these patients.[2]

Postoperative symptomatic hypocalcemia was reported in the literature.[3,9,16,19] Postoperative symptomatic hypocalcemia was generally observed within 3 days after surgery.[3] In our cases, they were followed closely in the postoperative period under prophylactic Ca replacement and close lab evaluation. The necessity of reoperation was related to the surgical technique due to the inability to remove the lesion completely.

In the literature, most pediatric case series included patients >18 years of age.[5,8-11] Parathyroid adenoma in pediatric patients has been limited to case reports and small series. Only

a small group of patients are symptomatic in childhood; there is no clinical guideline for PTA. Case reports and case series are significant for a better understanding of the nature of the disease and to improve management and follow-up. "Although there are patients with the same genetic mutations, why some of the cases were diagnosed earlier, and some remain silent till adulthood" is still unknown. "Might PTH secretion be different between childhood and adulthood patients?" is one of the unanswered questions. There are much more points that need to be clarified. As the distribution of signs and symptoms by age is known, it will be easier to carry out studies that illuminate the pathophysiological mechanism.

In conclusion, PTA should be considered in children older than the first decade with hypercalcemia. It should be kept in mind that most cases are asymptomatic at diagnosis. Suspected cases should undergo both US and scintigraphy to detect PTA. Patients should be carefully followed up for the risk of MEN syndrome. Early diagnosis prevents the patients from serious complications of hypercalcemia such as nephrocalcinosis, diabetes insipid, and arrhythmia. It is significant to perform surgery in centers experienced in parathyroidectomy to minimize postoperative complications.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ankara University (Approval No: I1-81-21, Date: 05.02.2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.B., Z.S.; Design – Z.A, E.O.; Supervision – M.B, Z.S.; Data Collection and/or Processing – S.C., S.K., G.S.; Analysis and/or Interpretation – S.C., E.O., Z.S.; Literature Review – S.C., G.S., S.K., X.X.; Writing – S.C., Z.S., M.B.; Critical Review – M.B., Z.S, Z.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Dutta A, Pal R, Jain N, et al. Pediatric parathyroid carcinoma: a case report and review of the literature. *J Endocr Soc*. 2019;3(12):2224-2235. [CrossRef]
2. Roizen J, Levine MA. Primary hyperparathyroidism in children and adolescents. *J Chin Med Assoc*. 2012;75(9):425-434. [CrossRef]
3. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. *Lancet*. 2018;391(10116):168-178. [CrossRef]
4. Jamshidi R, Egan JC, eds. Pediatric parathyroid disease. *Semin Pediatr Surg*. Amsterdam: Elsevier; 2020;29(3):150923. [CrossRef]
5. Rampp RD, Mancilla EE, Adzick NS, et al. Single gland, ectopic location: adenomas are common causes of primary hyperparathyroidism in children and adolescents. *World J Surg*. 2020;44(5):1518-1525. [CrossRef]
6. Baloch Z, Livolsi V. Parathyroids morphology and pathology. *The Parathyroids*. USA: Elsevier; 2015:23-36.
7. Stokes VJ, Nielsen MF, Hannan FM, Thakker RV. Hypercalcemic disorders in children. *J Bone Miner Res*. 2017;32(11):2157-2170. [CrossRef]
8. Allo M, Thompson NW, Harness JK, Nishiyama RH. Primary hyperparathyroidism in children, adolescents, and young adults. *World J Surg*. 1982;6(6):771-776. [CrossRef]
9. Kollars J, Zarroug AE, van Heerden J, et al. Primary hyperparathyroidism in pediatric patients. *Pediatrics*. 2005;115(4):974-980. [CrossRef]
10. Loh KC, Duh QY, Shoback D, Gee L, Siperstein A, Clark OH. Clinical profile of primary hyperparathyroidism in adolescents and young adults. *Clin Endocrinol (Oxf)*. 1998;48(4):435-443. [CrossRef]
11. Hsu SC, Levine MA. Primary hyperparathyroidism in children and adolescents: the Johns Hopkins Children's Center experience 1984-2001. *J Bone Miner Res*. 2002;17(2):N44.
12. Demir K, Konakçı E, Özkaya G, et al. New features for child metrics: further growth references and blood pressure calculations. *J Clin Res Pediatr Endocrinol*. 2020;12(2):125-129. [CrossRef]
13. Neyzi O, Bundak R, Gökçay G, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. *J Clin Res Pediatr Endocrinol*. 2015;7(4):280-293. [CrossRef]
14. Venail F, Nicollas R, Morin D, et al. Solitary parathyroid adenoma: a rare cause of primary hyperparathyroidism in children. *Laryngoscope*. 2007;117(5):946-949. [CrossRef]
15. Harman CR, van Heerden JA, Farley DR, Grant CS, Thompson GB, Curlee K. Sporadic primary hyperparathyroidism in young patients: a separate disease entity? *Arch Surg*. 1999;134(6):651-655. [CrossRef]
16. Sharanappa V, Mishra A, Bhatia V, et al. Pediatric primary hyperparathyroidism: experience in a tertiary care referral center in a developing country over three decades. *World J Surg*. 2020:1-8.
17. Rapaport D, Ziv Y, Rubin M, Huminer D, Dintsman M. Primary hyperparathyroidism in children. *J Pediatr Surg*. 1986;21(5):395-397. [CrossRef]
18. Mallet E, Working Group on Calcium Metabolism. Primary hyperparathyroidism in neonates and childhood. The French experience (1984-2004). *Horm Res*. 2008;69(3):180-188. [CrossRef]
19. Li CC, Yang C, Wang S, Zhang J, Kong XR, Ouyang J. A 10-year retrospective study of primary hyperparathyroidism in children. *Exp Clin Endocrinol Diabetes*. 2012;120(4):229-233. [CrossRef]