ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Clinical Features of a Group of Adolescents Diagnosed with Primary Hyperparathyroidism

Primer Hiperparatiroidizm Tanılı Bir Grup Adolesanın Klinik Özellikleri

Ömer Günbey (0000-0002-8888-2954), Firdevs Dilara Paksoy (0000-0002-5052-6778), Nurdan Yıldırım Acar (0009-0000-7680-1830), Deniz Ökdemir (0000-0003-3618-8167), İhsan Esen (0000-0003-1700-6778)

Fırat University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Elazığ, Türkiye

Cite this article as: Günbey Ö, Paksoy FD, Yıldırım Acar N, Ökdemir D, Esen İ. Clinical features of a group of adolescents diagnosed with primary hyperparathyroidism. J Curr Pediatr. 2025;23(2):80-5

Abstract

Introduction: Primary hyperparathyroidism (PHPT) is a rare disease in children. There are a limited number of publications on pediatric PHPT. In this study, we present the clinical characteristics of a group of children with PHPT.

Materials and Methods: The hospital records of seven adolescents diagnosed with PHPT and who underwent surgery at our clinic between 2013 and 2023 were retrospectively reviewed.

Results: The study group consisted of seven adolescents, three of whom were girls, with a median age of 14 years (range: 13-17). The most common presenting symptom was myalgia (3/7). One patient with abdominal pain was diagnosed with acute pancreatitis. Three patients had nephrolithiasis secondary to hypercalcemia. Ultrasonography detected adenomas in five patients (71%). Scintigraphic imaging revealed isolated parathyroid adenomas ranging from 0.5 to 2.0 cm in size in all patients. The most common lesion location was the lower part of the right thyroid lobe (3/7). All patients underwent surgical excision of the parathyroid adenoma. Preoperative median calcium level was 12.0 mg/dL (10.6-13.1), and median parathyroid hormone (PTH) level was 340 pg/mL (98-803). Postoperatively, median calcium level decreased to 8.6 mg/dL (8.3-9.1), and median PTH level decreased to 38.3 pg/mL (12.2-73.0). No postoperative complications were observed. Pathology results confirmed parathyroid adenoma in all cases. All patients remained in remission after at least six months of follow-up.

Conclusion: This study indicates that children with PHPT are often diagnosed based on non-specific symptoms. Isolated parathyroid adenomas detected through imaging can be successfully treated with surgery.

Keywords
Adolescent, hypercalcemia, parathyroid adenoma, primary hyperparathyroidism

Anahtar kelimeler
Adolesan, hiperkalsemi, paratiroid adenomu, primer hiperparatiroidizm

Received/Geliş Tarihi : 02.01.2025
Accepted/Kabul Tarihi : 28.04.2025
Published Date/ Yayınlanma Tarihi : 21.08.2025

DOI:10.4274/jcp.2025.51423

Address for Correspondence/Yazışma Adresi: Ömer Günbey, Fırat University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Elazığ, Türkiye
E-mail: omergunbey50@gmail.com

Öz

Giriş: Çocuklarda primer hiperparatiroidizm (PHPT) nadir görülen bir hastalıktır. PHPT'li çocuklara dair sınırlı sayıda yayın bulunmaktadır. Bu yazıda PHPT'li bir grup çocuğun klinik özellikleri sunulmuştur.

Gereç ve Yöntem: Kliniğimizde 2013-2023 yılları arasında PHPT tanısı alıp cerrahi tedavi uygulanan 7 adolesanın hastane dosyaları geriye dönük olarak incelendi.

Bulgular: Çalışma grubunu ortanca yaşı 14 yıl (13-17 arasında) olan, üçü kız yedi adolesan oluşturmaktaydı. En sık başvuru şikayeti miyaljiydi (3/7). Karın ağrısı olan bir hastamız akut pankreatit tanısı aldı. Üç hastada hiperkalsemiye bağlı nefrolitiyazis tespit edildi. Ultrasonografi ile beş hastada (%71) adenom görüntülendi. Sintigrafik incelemede tüm hastalarda boyutları 0,5 ile 2,0 cm arasında olan izole paratiroid adenomu ile uyumlu lezyonlar tespit edildi. En sık lezyon lokalizasyonu sağ tiroid lobunun alt kısmıydı (3/7). Tüm hastalarda cerrahi olarak paratiroid adenom eksize edildi. Preoperatif ortanca kalsiyum düzeyi 12,0

mg/dL (10,6-13,1), ortanca paratiroid hormon düzeyi 340 pg/mL (98-803) idi. Postoperatif ortanca kalsiyum değeri 8,6 mg/dL (8,3-9,1)'ye, ortanca paratiroid hormon değeri 38,3 pg/ml (12,2-73,0)'ye geriledi. Hastalarımızda postoperatif komplikasyon gelişmedi. Patoloji sonuçları tüm hastalarda paratiroid adenom olarak raporlandı. En az 6 aylık takip sürecinde tüm hastalar remisyonda idi.
Sonuç: Bu çalışma grubunda PHPT'li çocukların sıklıkla özgün olmayan yakınmalar ile tanı aldığı, görüntüleme ile saptanan izole paratiroid adenomlarının cerrahi ile başarı ile tedavi edilebildiği gözlendi.

Introduction

Primary hyperparathyroidism (PHPT) is a disease associated with hypercalcemia in which serum parathyroid hormone (PTH) levels are inappropriately normal or elevated as a result of excessive PTH secretion from one or more of the four parathyroid glands (1). In most cases, PHPT is caused by a single parathyroid adenoma. Parathyroid carcinoma is a relatively rare pathology (2). PHPT is usually isolated and not genetically inherited (3). The annual incidence of PHPT is estimated to be 3 per 10,000 in adults aged 50 to 60 years, and it is 2 to 3 times more common in women than in men (1). PHPT is relatively rare in pediatric patients, with an estimated incidence of 2 to 5 cases per 100,000 individuals (2).

Hypercalcemia associated with hyperparathyroidism can cause constipation, bone pain, fatigue, depression and formation of renal stones (2,4). It can also negatively affect the myocardium and lead to fatal arrhythmias such as short QT syndrome, ventricular tachycardia, and ventricular fibrillation (4). Hyperparathyroidism can also lead to osteoporosis and increased susceptibility to the development of fractures (2). Since the symptoms are often nonspecific and hypercalcemia sometimes may occur intermittently, the diagnosis is sometimes delayed until end-organ damage occurs (5,6). In this study, we present our experience with seven pediatric PHPT cases, including their clinical spectrum and postoperative follow-up data.

Materials and Methods

Study Design

The medical records of seven patients under the age of 18 diagnosed with PHPT between 2013 and 2023 at the pediatric endocrinology clinic of our hospital were retrospectively reviewed. The study was approved by the Fırat University Non-Interventional Research Ethics Committee (date: 11.09.2024, approval number: 2024/12-41). The patients' age, presenting symptoms, physical examination findings at admission, and relevant personal and family medical history were evaluated Serum calcium, inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH), creatinine, 25(OH) vitamin D, urinary calcium, and urinary creatinine levels were recorded. The urinary calcium-to-creatinine ratio was calculated. Hypocalciuria was defined as a spot urine calcium/creatinine ratio <0.04 mg/mg, and hypercalciuria as a ratio >0.22 mg/mg (7). Ultrasonographic and scintigraphic findings were documented. Preoperative and postoperative clinical features were also evaluated.

Statistical Analysis

The data obtained within the scope of the study were expressed with descriptive statistics. Categorical variables were expressed as percentages. Since the number of patients in our case series is low, continuous variables were presented as median (min-max). All statistical calculations were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Our patient population with a median age of 14 (minimum 13, maximum 17 years) consisted of four boys and three girls. None of them had a family history of primary hyperparathyroidism. There was no history of radiation exposure.

The most common presenting complaint was myalgia (3/7). The amylase level was 1508 U/L in one female patient (# 4) diagnosed with acute pancreatitis secondary to hypercalcemia with abdominal pain. Magnetic resonance cholangiopancreatography (MRCP) revealed the presence of a normal pancreas. Patient with pancreatitis had no PHPT-associated bone lesions, nephrolithiasis or nephrocalcinosis was not noted with the ultrasonographic examination of the urinary system. The patient's amylase level normalized following preoperative intravenous hydration. This patient with pancreatitis was previously presented as a case report (8). Except for one patient, all patients presented to our center within 1 to 3 months after the detection of hypercalcemia and were evaluated for hyperparathyroidism. It was learned that one patient had been found to have hypercalcemia in tests conducted approximately 1.5 years before admission to our clinic and had received treatment at a urology clinic

for nephrolithiasis. Additionally, nephrolithiasis secondary to hypercalcemia was detected in two more patients. Clinical and imaging characteristics of the patients are summarized in Table 1.

Neck ultrasonography (US) and parathyroid scintigraphy were performed in all patients. US revealed hypoechoic lesions suspicious for adenoma in five (71%) patients. Scintigraphic examination of parathyroid glands disclosed the presence of parathyroid adenoma in all patients (100%). Most commonly adenoma was localized in the lower part of the right thyroid lobe in three patients (43%). The largest adenoma was measured as 3 cm, and the smallest one as 0.5 cm on US. On scintigraphic examination, the largest and the smallest adenomas were measured as 2.0 cm and 0.5 cm, respectively (Table 1).

In these patients, *RET* gene sequence analysis for multiple endocrine neoplasia (MEN) syndromes could be performed in two patients and no mutation was found.

Our four patients had high urinary calcium/creatinine values. Calcium/creatinine ratio of two patients was within the normal range. One patient who did not undergo urine tests could not be evaluated.

All patients received preoperative IV hydration treatment for hypercalcemia. Diuretics were used after adequate hydration was achieved. Considering the risk of postoperative hypocalcemia, vitamin D deficiency was investigated. Patients with low vitamin D levels or hypercalciuria were started on cholecalciferol before surgery. Parathyroid adenomas were surgically excised in all patients. Patients with postoperative hypocalcemia were added oral calcium treatment in addition to cholecalciferol. If postoperative calcium was normal, they were treated only cholecalciferol. Bisphosphonate treatment was not given to any patient. All patients were followed up closely postoperatively. Postoperative normalized PTH values increased again in four patients at the third month follow-up.

However, calcium values were normal at the third postoperative month. Three of these patients had low preoperative 25 OH vitamin D levels. In one patient (# 3), PTH value remained elevated despite normal 25 OH vitamin D levels until the 6th postoperative month. Prophylactic treatments were tapered and discontinued under close monitoring of laboratory values. Patients were re-evaluated at the sixth postoperative month. Physical examination and laboratory findings were normal at the 6th postoperative month. Preoperative and postoperative laboratory tests of the patients are given in Table 2.

Postoperative complications did not develop in our patients. The pathology result of one patient (# 2) was reported as lymph node. Postoperative calcium and PTH values continued to rise. Scintigraphy was performed again

Table 1. Clinical and imaging characteristics of the patients with primary hyperparathyroidism

Case	Gender	Age (years)	Symptoms	End-organ damage	Lesion detected by scintigraphy	Lesion detected by ultrasonography
1	Female	13	Abdominal pain	Nephrolithiasis	+	+
2	Male	13	Flank pain	Nephrolithiasis	+	+
3	Male	14	Myalgia, headache, lassitude, constipation	Nephrolithiasis	+	+
4	Female	14	Abdominal pain, flank pain, vomiting	Pancreatitis	+	+
5	Male	16	Myalgia, halitosis, lassitude	None	+	+
6	Female	17	Myalgia	None	+	-
7	Male	17	Nausea, inability to gain weight	None	+	-

Table 2. Biochemical parameters of the patients with primary hyperparathyroidism

	At admission	Postoperative			
		0. day	1. day	3. month	6. month
Calcium (mg/dL)	12.0 (10.6-13.1)	9.5 (8.0-9.9)	8.6 (8.3-9.1)	9.4(8.6-10.3)	10.0 (9.4-10.4)
Phosphorus (mg/dL)	2.8 (1.9-3.9)		2.8 (1.8-3.5)	3.8 (3.6-5.2)	4 (3.4-6.6)
ALP (U/L)	207 (149-359)	321 (217-424)	298 (202-394)	108 (53-179)	127 (51-163)
PTH (pg/mL)	340 (98-803)	26.6 (2-661)	38.3 (12.2-73)	120 (28-148)	59.5 (28.3-82.1)
25OH vitamin D (µg/dL)	19.5 (5.3-36.4)				20.9 (5.6-29.4)

ALP: Alkaline phosphatase; PTH: Parathyroid hormone, variables are expressed as median (minimum-maximum) values

and the patient was operated for the second time. Operated on a second time patient calcium and PTH values decreased. The pathology result was reported as parathyroid adenoma.

Discussion

In this study, we present the clinical and laboratory features of a group of adolescents with primary hyperparathyroidism (PHPT), a rare clinical entity in childhood.

In the literature, the age of onset of PHPT is frequently reported to be 55-60 years (1). The reason for the rarity of PHPT in childhood is unknown. In the literature on pediatric PHPT, Roizen and Levine reviewed the case series of approximately 340 patients until 2012 (2). A scarce number of case series including at most 86 patients have been published after 2012 (9-12). A clinical guideline for parathyroid adenoma in pediatric patients has not yet been established. Case series are important for better follow-up and treatment of the disease and establishment of future guidelines.

In a recently reported pediatric PHPT case series of 10 patients, all patients were symptomatic (10). In our study, all patients were symptomatic, consistent with the literature. Most young patients with PHPT typically present with skeletal complications of hypercalcemia and/or symptoms of nephrolithiasis (2). The most common symptoms in our patients were abdominal pain accompanied with nephrolithiasis, and musculoskeletal pain. In a case series by Li et al. (13) genu valgum and bone fractures were reported in patients with PHPT. Bone lesions were not reported in a case series from our country. We did not observe bone lesions in our patients which presumably may be related to the duration of hyperparathyroidism (9).

The relationship between PHPT and pancreatitis is still unclear. One study reported that the incidence of pancreatitis in patients with PHPT was approximately 30 times higher than in the general population (14). It has been thought that hypercalcemia may cause activation of intrapancreatic trypsin and pancreatic damage leading to the development of pancreatitis (15). The prevalence of acute pancreatitis in PHPT is between 1.5% and 13% (16). In one study, acute pancreatitis was detected in two of 14 patients (17). Consistent with the literature, one of our seven patients (14%) previously reported by us as a case report was diagnosed with acute pancreatitis (8). In most patients with PHPT, pancreatitis symptoms improve after surgical treatment (14). Similarly, the most common pathology in children and adolescents with PHPT is a single parathyroid adenoma (2,12). Consistent with the literature, all of our patients had a single parathyroid adenoma. The only curative treatment for PHPT associated with isolated parathyroid adenoma is excision of the adenoma (12). In a recently published case series, one patient required reoperation (9). In one of our patients, postoperative calcium and PTH values did not regress despite intraoperative removal of a lesion thought to be compatible with parathyroid adenoma. The pathology result of this patient was reported as lymph node. Scintigraphy was performed again and the patient was operated for the second time and the adenomectomized patient went into remission. Consistent with the literature, all of our patients achieved postoperative cure. Most frequently the adenoma is located in the lower lobe of the thyroid (9,10). Consistent with the literature data, in our patients, parathyroid adenomas were localized adjacent to the lower lobe of thyroid.

The first-line modalities for imaging parathyroid glands are ultrasound and/or 99m Tc sestamibi scintigraphy (4). On ultrasound, parathyroid adenomas appear as hypoechoic and often enlarged nodular lesions (4). On scintigraphy, hyperfunctioning glands show greater uptake of the technetium radioisotope (4).

A meta-analysis reported a diagnostic sensitivity of 78% for high-resolution US and 88% for dual-phase Tc-99m sestamibi scintigraphy (18). However, Tc-99m sestamibi parathyroid imaging has a limited capacity to detect small parathyroid adenomas or multiglandular lesions, especially in cases of preoperative normocalcemia (19). In adult patients, 4D computed tomography has become an increasingly used imaging modality and has been reported to have higher diagnostic sensitive than scintigraphy, especially for multiglandular disease (20,21). The calculated radiation dose of 4D computed tomography is estimated to be approximately 60 times higher than that of 99mTc- sestamibi SPECT which limits the use of 4D computed tomography in younger patients who are at higher risk of developing radiation-related cancers (22). Combined ultrasonography and scintigraphic imaging increases the probability of lesion localization and improves diagnostic sensitivity (23). In our two patients, no adenoma was detected by ultrasound. Scintigraphy detected adenomas in all patients.

The etiology of PHPT includes multigland hyperplasia resulting from germline mutations in the *MENIN, RET*, and *CDKN1B* (encoding p27Kip1) genes; single parathyroid adenomas that represent monoclonal neoplasms, many of which are associated with somatic mutations in *MENIN* or *PRAD1 gene;* and distinct parathyroid adenomas due to germ-line or somatic mutations in *HRPT2* gene (CDC 73), which have a predisposition to parathyroid carcinoma

(2). Multiple endocrine neoplasia type 1, or MEN1 (OMIM 131099), is the most common cause of inherited PHPT. PHPT is present in more than 90% of patients with MEN1 (2). Some patients with MEN1 who do not have mutations in *MENIN* may have mutations in *CDKN1B*, which encodes the cyclin-dependent kinase inhibitor 1B (2). PHPT is relatively uncommon in MEN2a (OMIM 171399), occurring in only 20–30% of patients, and almost never occurs in MEN2b (OMIM 162299) (2). PHPT is less severe in patients with MEN2a than in patients with MEN1. The highest prevalence of PHPT occurs in patients who carry the codon 634 *RET* gene mutation (2). Germline mutations of the *HRPT2* gene cause the hyperparathyroidism-jaw tumor (HPT-JT) syndrome (OMIM 145010). HPT-JT syndreme is an uncommon autosomal dominant syndrome characterized by PHPT due to parathyroid adenomas and fibro-osseous lesions of the maxilla and mandible (2). *RET* gene analysis performed on two of our patients yielded normal results.

Preoperative vitamin D repletion is advised and should be performed carefully in patients with hypercalciuria (23). The frequency of postoperative hypocalcemia has been reported to be approximately 50% in the literature. Severe hypocalcemia is rarely seen (2,23). Patients may require temporary postoperative calcium administration and calcitriol to avoid such symptoms (23). Patients with low vitamin D levels were started on cholecalciferol treatment before surgery. Postoperatively, biochemical hypocalcemia was detected in four of seven patients. These patients were closely monitored and treated with oral calcium and cholecalciferol. Oral calcium treatment was discontinued once serum calcium levels stabilized.

Study Limitations

The study was conducted retrospectively based on a file review, and the sample size was relatively small.

Conclusion

In conclusion, the diagnosis of pediatric hyperparathyroidism may be delayed until end-organ damage develops because symptoms are often nonspecific and sometimes hypercalcemia is episodic. In this study group, we have observed that children with PHPT were often diagnosed with nonspecific complaints and isolated parathyroid adenomas detected by imaging can be successfully treated with surgery.

Ethics

Ethics Committee Approval: The study was approved by the Fırat University Non-Interventional Research Ethics Committee (date:11.09.2024, approval number: 2024/12-41).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Griebeler ML, Kearns AE, Ryu E, Hathcock MA, Melton LJ 3rd, Wermers RA. Secular trends in the incidence of primary hyperparathyroidism over five decades (1965-2010). Bone. 2015;73:1-7.
2. Roizen J, Levine MA. Primary hyperparathyroidism in children and adolescents. J Chin Med Assoc. 2012;75:425-34.
3. Arslan K, Törel Ergür A, Pampal A, Kaymaz E Parathyroid hormone dependent hypercalcemia in childhood: due to three cases. J Med Palliat Care. 2021;2:28-34.
4. Jamshidi R, Egan JC. Pediatric parathyroid disease. Semin Pediatr Surg. 2020;29:150923. Epub 2020 May 17.
5. Damiani D, Aguiar CH, Bueno VS, Montenegro FL, Koch VH, Cocozza AM, et al. Primary hyperparathyroidism in children: patient report and review of the literature. J Pediatr Endocrinol Metab. 1998;11:83-6.
6. Kollars J, Zarroug AE, van Heerden J, Lteif A, Stavlo P, Suarez L, et al. Primary hyperparathyroidism in pediatric patients. Pediatrics. 2005;115:974-80.
7. Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. J Pediatr. 1993;123:393-7.
8. Esen İ, Demir F, Deveci UA. Pediatric case of acute pancreatitis as initial manifestation of primary hyperparathyroidism. Kuwait Medical Journal. 2016;48:245-8.
9. Kızılcan Çetin S, Şıklar Z, Aycan Z, Özsu E, Ceran A, Erisen Karaca S, et al. Clinical profile of parathyroid adenoma in children and adolescents: a single-center experience. Turk Arch Pediatr. 2023;58:56-61.
10. Boro H, Khatiwada S, Alam S, Kubihal S, Dogra V, Malla S, et al. The spectrum of manifestations of primary hyperparathyroidism in children and adolescents. Pediatr Endocrinol Diabetes Metab. 2022;28:178-87.
11. Sharanappa V, Mishra A, Bhatia V, Mayilvagnan S, Chand G, Agarwal G, et al. Pediatric primary hyperparathyroidism: experience in a tertiary care referral center in a developing country over three decades. World J Surg. 2021;45:488-95.
12. Rampp RD, Mancilla EE, Adzick NS, Levine MA, Kelz RR, Fraker DL, et al. Single gland, ectopic location: adenomas are common causes of primary hyperparathyroidism in children and adolescents. World J Surg. 2020;44:1518-25.
13. 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;120:229-33.

14. Bai HX, Giefer M, Patel M, Orabi AI, Husain SZ. The association of primary hyperparathyroidism with pancreatitis. J Clin Gastroenterol. 2012;46:656-61.
15. Mithöfer K, Fernández-del Castillo C, Frick TW, Lewandrowski KB, Rattner DW, et al. Acute hypercalcemia causes acute pancreatitis and ectopic trypsinogen activation in the rat. Gastroenterology. 1995;109:239-46.
16. Misgar RA, Mathew V, Pandit K, Chowdhury S. Primary hyperparathyroidism presenting as recurrent acute pancreatitis: a case report and review of literature. Indian J Endocrinol Metab. 2011;15:54-6.
17. Bhadada SK, Bhansali A, Dutta P, Behera A, Chanukya GV, Mittal BR. Characteristics of primary hyperparathyroidism in adolescents. J Pediatr Endocrinol Metab. 2008;21:1147-53.
18. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg. 2005;132:359-72.
19. Merlino JI, Ko K, Minotti A, McHenry CR. The false negative technetium-99m-sestamibi scan in patients with primary hyperparathyroidism: correlation with clinical factors and operative findings. Am Surg. 2003;69:225-9.
20. Hoang JK, Williams K, Gaillard F, Dixon A, Sosa JA. Parathyroid 4D-CT: multi-institutional International Survey of Use and Trends. Otolaryngol Head Neck Surg. 2016;155:956-60.
21. Galvin L, Oldan JD, Bahl M, Eastwood JD, Sosa JA, Hoang JK. Parathyroid 4D CT and scintigraphy: what factors contribute to missed parathyroid lesions? Otolaryngol Head Neck Surg. 2016;154:847-53.
22. Mahajan A, Starker LF, Ghita M, Udelsman R, Brink JA, Carling T. Parathyroid four-dimensional computed tomography: evaluation of radiation dose exposure during preoperative localization of parathyroid tumors in primary hyperparathyroidism. World J Surg. 2012;36:1335-9.
23. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016;151:959-68.