









Case Report

## A childhood primary hyperparathyroidism due to parathyroid adenoma: Atypical presenting with leg pain and normocalcemia

### Atipik bacak ağrısı ve normokalsemiyle sunulan paratiroid adenomuna bağlı çocukluk çağı primer hiperparatiroidizmi

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#### ABSTRACT

Primary hyperparathyroidism (PHPT) is a rare disorder in childhood and adolescence. Parathyroid adenoma is the most common cause of PHPT. Laboratory findings mainly include hypercalcemia, hypophosphatemia, hypercalciuria and elevated parathormone levels, but if 25 hydroxyvitamin D levels are below 20 ng/mL, normal serum calcium can be observed. In this report, we presented a boy diagnosed with parathyroid adenoma, uncommon in childhood, with only leg pain symptoms other than hypercalcemia and hypercalciuria.

**Keywords:** Childhood, parathyroid adenoma, primary hyperparathyroidism, leg pain

#### ÖZET

Primer hiperparatiroidizm çocukluk çağı ve adölesan dönemde nadir olarak görülmektedir. Primer hiperparatiroidinin en sık sebebi paratiroid adenomudur. Laboratuvar bulguları; hiperkalsemi, hipofosfotemi, hiperkalsiüri ve artmış parathormondur. 25 hidroksi D vitamini seviyesi 20 ng/dl'nin altında ise normal serum kalsiyum seviyesi de gözlenebilir. Biz bu raporda hiperkalsemi ve hiperkalsiüri semptomu olmadan sadece bacak ağrısı ile başuran paratiroid adenomlu erkek çocuk olgusu sunduk.

**Keywords:** Çocukluk çağı, paratiroid adenomu, primer hiperparatiroidizm, bacak ağrısı

#### INTRODUCTION

Primary hyperparathyroidism (PHPT) is a generalized disorder of the metabolism of calcium, phosphate and bone. It is characterized by hypercalcemia, hypophosphatemia, and normal or high parathormone levels.

PHPT is less common in the pediatric population than in adults, with an estimated incidence of 1 per 200-300,000 and a prevalence of 2-5 in 100,000 (1,2). In adult PHPT, the female/male ratio is approximately 3:1.

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Gender distribution of pediatric PHPT appears to be nearly equal in contrast to adults (3). Primary hyperparathyroidism may arise from a parathyroid adenoma, parathyroid hyperplasia or parathyroid cancer. The etiology of hyperparathyroidism varies according to age group. PHPT may present within the first few days of life as severe neonatal hyperparathyroidism (NSHPT). In most cases, neonates with NSHPT have inactivating variations on both calcium-sensing receptor (CaSR) gene alleles, resulting in a complete or near-complete absence of functional CaSRs on parathyroid and other cells in the body. Childhood/adolescent PHPT is associated with either single or multiple parathyroid adenomas (3). In most cases, PHPT arises from a single benign parathyroid adenoma (90%). Multiple adenomas rarely occur in approximately 2-4% of cases (4). A parathyroid adenoma may occur alone or as a component of syndromes, such as MEN 1 and 2A. In many studies, PHPT occurs in approximately 15% of MEN1 and 8% of MEN2A syndrome (3).

The features of symptoms of PHPT vary according to age groups. In infancy, bone abnormalities, such as fractures, chest deformities, metaphysical irregularities, cortical dualization, and subperiosteal erosion, are observed in approximately 83% of the cases. In contrast, hypercalcemia, hypercalciuria, and related symptoms are observed in about 60% of children or adolescents. Detecting incidental hypercalcemia due to PHPT is infrequent in young patients. This report presented a boy diagnosed with parathyroid adenoma with only leg pain symptoms other than hypercalcemia and hypercalciuria. To our knowledge, our case is the only normocalcemic parathyroid adenoma case who presented only with leg pain in the literature.

### Case Report

A 12-year-old boy presented with 4-month history of pain in the right knee that was exaggerated with prolonged walking. His past medical history did not reveal any history of trauma, fractures, abdominal pain, anorexia, vomiting, constipation, headache, blurred vision, polyuria, fatigue, depression, irritability and renal stones. There were not any endocrine or skeletal disorders in his family history. On physical examination, his height was 137cm (-1.13 SD) and his weight was 35 kg (-0.41 SD). His vital signs were within normal range. In the patient's pubertal examination, bilateral testicular volumes were 2 ml and the penis length was 6 cm. The biochemical profile showed hypophosphatemia normocalcemia, elevated PTH and alkaline phosphatase (ALP) levels and a low 25(OH)D 3 level (Table 1). Ini-

ally, we considered the prediagnosis of rickets in the patient. However, the wrist radiograph of the patient was compatible with osteitis cystica (Picture 1). Skeletal X-rays also showed prominence in trabeculae and the loss of density in vertebrae. These findings suggested primary hyperparathyroidism in the foreground. Neck ultrasonography showed a parathyroid mass size of 13x7x27 mm posterior to the right lobe of the thyroid gland. In the Tc -99m MIBI scintigraphy taken the focal activity uptake observed in the early images near the right lobe posterior inferior of the thyroid gland continues in the late images. This appearance was interpreted as parathyroid adenoma.



**Figure 1.** The wrist radiograph. Circle indicates osteitis cystica in the fibula

Anterior pituitary hormones were performed to rule out other tumors and syndromes. Hormone profile was resulted as prolactin 6.36 ng/ml; cortisol 16,44 ng/ml (blood sample taken at 8 a.m.) and ACTH 16 pg/ml, in normal ranges. In the 4th month of follow-up, the patient developed hypercalcemia, and the serum calcium level increased to 13.5 mg/dl and phosphorus was detected as 3.9 mg/dl. Pamidronate treatment was administered due to unresponsive hypercalcemia to hydration alone. After treatment, calcium level decreased to 11.1 mg/dl phosphorus level was 2.5 mg/dl and the patient was operated on. Right parathyroidectomy was performed. A tumor of 1.53 gr weight was resected. The pathological diagnosis resulted in parathyroid adenoma.

In postsurgical laboratory analysis, PTH was 31 pg/ml, serum calcium was 7.7 mg/dl, and phosphate was 2.5 mg/dl. Chvostek's sign was determined on physical examination. Intravenous administration of calcium was performed for the hungry bone syndrome. Oral

calcium supplementation and calcitriol were continued. One month after the operation, the patient's medications were discontinued and bone pain complaints were over. The patient's parents' consent was obtained for this case study.

## DISCUSSION

PHPT is infrequent and associated with severe morbidity in children and adolescents. In adults, PHPT is usually an asymptomatic disorder that presents as incidentally discovered hypercalcemia. In the juvenile population (age 0-25 y), by contrast, PHPT is uncommon and clinically symptomatic (5,6). Given that adults have more frequent routine examinations than children is one of the important hypotheses explaining this situation. Therefore, PHPT is identified in younger patients only when they become symptomatic. Alternatively, it is also conceivable that juvenile PHPT is a different disease, and specifically, a more aggressive disease than adult PHPT.

Recent knowledge about this topic is insufficient since current literature mostly provides case reports or case series of patients with PHPT in youths and only one meta-analysis dealing with a comparison of the biochemistry of PHPT between youths and the adults exists (7). Although it is still rare in children and adolescents (2-5 cases in 100.000), there is an increasing trend of diagnosed and treated patients in these age groups (7).

Clinical findings of primary hyperparathyroidism may vary according to age groups. Skeletal abnormalities (82%), hypotonicity (55%), failure to thrive (43%) and respiratory problems (22%) in newborns have been described in published series, which may occur as hypercalciuria (60%), bone diseases (43%), kidney stones (39%) in the childhood and adolescent age group, or it may be asymptomatic (14%) (3). In our case, there was only leg pain symptom. In the current literature, there is only one case report of a patient who applied with the complaint of leg pain. In this case, a 17-year-old male patient was admitted to the hospital with the complaint of severe leg pain. However, the patient had a previous history of trauma to his shoulder and his leg and Ca value of this individual was 15.3 mg/dl. In 2021, Oh et al. (15) presented three patients with PHPT who manifested variable clinical features of hypercalcemia. The first and second patients each had a parathyroid adenoma and presented with abdominal pain caused by pancreatitis and a ureter stone, respectively. The third patient had an ectopic mediastinal parathyroid adenoma

and presented with gait disturbance and weakness in the lower extremities. Primary hyperparathyroidism due to giant parathyroid adenoma was detected in the patient who was examined (8). Therefore, to our knowledge, we reported the first patient in the literature who presented with leg pain had a Ca value within normal range but was diagnosed with primary hyperparathyroidism due to parathyroid adenoma.

In PHPT, there is an increased or normal level of parathormone despite an increased serum calcium level. However, it has been reported that normocalcemia may be the incipient period of PHPT where calcium levels are in the normal range or do not rise yet, and it may advance to overt PHPT (9). It is called normocalcemic PHPT. In a large series of adult study conducted in 2016, patients with normocalcemic hyperparathyroidism were followed for six years. In total, 36 of 187 patients who were normocalcemic for more than six years became hypercalcemic (19%), and 11 of these 36 patients had parathyroid adenoma (10). In children, studies on normocalcemic primary hyperparathyroidism are limited to individual cases (11). Normocalcemic patients should be monitored long-term basis, as it is impossible to anticipate when and which normocalcemic patients will become hypercalcemic. Our case was normocalcemia, and he had no hypercalcemic symptoms initially. He had only complained about his leg pains. Serum calcium level increased in about four months. This was an interesting case of hyperparathyroidism with an atypical presentation. On the other hand, if children have vitamin D deficiency, they may be normocalcemic or hypocalcemic and parathormone levels may increase secondary to this condition. Even some patients with PHPT may have rickets findings in their radiological images. In 2013, Dutta et al. (12) reported hypercalcemia after vitamin D replacement in a 12-year-old girl with primary hyperparathyroidism who presented with features of rickets and had low 25OHD (8.7 ng/mL). Similarly, Kataria et al. (13) observed rickets as a presentation of primary hyperparathyroidism. In the case reported in 2019, hypocalcemia, hypophosphatemia, low vitamin D level and high parathormone levels were detected. Rickets findings, such as genu varum, were found in the physical examination of the patients. After findings of hyperparathyroidism were detected in the radiographs, the patient was diagnosed with PHPT (14). Our patient also had low vitamin D levels and his calcium level was normal initially. At first, we thought that the instance had hyperparathyroidism was secondary to vitamin D deficiency in the patient because rickets is more common than PHPT. However, we detected oste-

itis cystica, a sign of PHPT. Therefore, we think that carefully evaluating bone radiographs in such patients is essential for an accurate and exact diagnosis. Furthermore, in a child with rickets, lack of improvement or hypercalcemia following vitamin D supplementation may be warning signs for further evaluation to rule out PHPT.

In conclusion, although parathyroid adenoma is uncommon in childhood, it may present without calcium elevation, a sign of hyperparathyroidism and only with nonspecific symptoms, such as leg pain without calcium elevation. If a patient with PHPT has concomitant vitamin D deficiency, it should be kept in mind that normocalcemia may be present. Nonspecific leg pain may also suggest a severe calcium metabolism disorder. Pediatricians need to evaluate the patient in detail to make the correct diagnosis.

#### Conflict of Interest / Çıkar Çatışması

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