Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 62; Numer/Number 4/2011
ISSN 0423–104X

Primary hyperparathyroidism: a rare endocrinopathy in children. Two case reports

Pierwotna nadczynność przytarczyc — rzadka endokrynopatia u dzieci. Opis dwóch przypadków

Agnieszka Walczyk[1], Mieczysław Szalecki[2–4], Aldona Kowalska[1]

[1]*Department of Endocrinology and Nuclear Medicine, Hollycross Cancer Centre, Kielce, Poland*
[2]*Department of Endocrinology and Diabetology, Children's Memorial Health Hospital, Warsaw, Poland*
[3]*Faculty of Health Sciences, Jan Kochanowski University, Kielce, Poland*
[4]*Department of Paediatric Endocrinology and Diabetology, Children's Hospital, Kielce, Poland*

Abstract

Primary hyperparathyroidism (PHPT) is thought to be a common disease in adults. However, it is a rare endocrine disorder in children and adolescents. We report two cases of primary hyperparathyroidism in children diagnosed at the Department of Endocrinology and Diabetes (E&D) in the Children's Hospital (ChH), Kielce. The clinical course of the disease in these cases was fundamentally dissimilar, which confirms the observation that this rare endocrinopathy in children presents various clinical profiles, leading to diagnostic difficulties. In the first case, the severe course of PHPT was observed with signs suggesting a hypercalcemic crisis. In the second case, the patient was in a good condition with a mild hypercalcemia and symptoms limited to the skeleton, due to early identification of the disease. We believe these cases indicate the significant role of calcemia determination as a screening test in the diagnosis of PHPT, including in children. **(Pol J Endocrinol 2011; 62 (4): 346–350)**

Key words: *primary hyperparathyroidism in children, hypertension, diabetes*

Streszczenie

Pierwotna nadczynność przytarczyc (PHPT) jest częstą chorobą układu dokrewnego u dorosłych i raczej rzadką wieku dziecięcego. W pracy przedstawiono dwa przypadki PHPT u dzieci zdiagnozowane na Oddziale Endokrynologiczno-Diabetologicznym Wojewódzkiego Specjalistycznego Szpitala Dziecięcego w Kielcach. Przebieg kliniczny choroby w obu przypadkach jest istotnie odmienny, co potwierdza obserwację, że ta rzadka u dzieci endokrynopatia może przybierać różny obraz i stanowić trudny problem diagnostyczny. W pierwszym choroba przebiegała od początku burzliwie, z objawami wręcz przełomu hiperkalcemicznego. W drugim PHPT rozpoznano wcześnie, stan dziecka był dobry, z umiarkowaną hiperkalcemią, objawami ograniczonymi do kośćca. Potwierdza to hipotezę o istotnej roli oznaczania kalcemii jako badania przesiewowego w diagnostyce PHPT, również u dzieci. **(Endokrynol Pol 2011; 62 (4): 346–350)**

Słowa kluczowe: *pierwotna nadczynność przytarczyc u dzieci, nadciśnienie tętnicze, cukrzyca*

Introduction

Primary hyperparathyroidism (PHPT) is thought to be a common disease in adults. The incidence of PHPT in the Polish population is estimated to be up to 30 cases in every 100,000 [1].

However, it is a rare endocrine disorder in children and adolescents, with a suggested incidence of 2–5 in every 100,000 [2]. The clinical manifestations of PHPT are highly heterogenous — from the asymptomatic forms, through mildly symptomatic, up to a severe disease with end-organ damage or life-threatening hypercalcemic crisis [1, 2].

Serum calcium level is still not a frequent screening examination in children and adolescents. For this reason, in contrast to adults, 73–94% of PHPT cases in young patients are recognised as a symptomatic, advanced disease with multi-organ changes [2–6].

We report two cases of primary hyperparathyroidism in children diagnosed in the Department of Endocrinology and Diabetes (E&D) at the Provincial Specialist Children's Hospital (PSChH) in Kielce between 2000 and 2010. The clinical course of the disease in the two cases was fundamentally dissimilar, which confirms the observation that this rare endocrinopathy in children presents various clinical profiles, leading to diagnostic difficulties.

Agnieszka Walczyk MD, Department of Endocrinology and Nuclear Medicine, Hollycross Cancer Centre, ul. S. Artwińskiego 3, 25–734 Kielce, Poland, tel: +48 (41) 367 42 10, fax: +48 (41) 345 68 82, e-mail: a.walczyk@post.pl

Case reports

Case no. 1

A boy aged 15 years one month was admitted in July 2002 to the Department of PE&D in Kielce with a diagnosis of hypertension. The patient's history included: gradual increasing of his overweight and sporadic infections. A month before admission, his right knee had been operated on due to valgity. After two weeks, he was hospitalised in the neurological department because of syncope and convulsions. A CT brain scan and electroencephalogram showed no abnormalities, but hypertension ranging from 190/90 to 150/90 was found. On admission to the Department of E&D, physical examination found a medium general condition, blood pressure 165/100–180/120, overweight (100.5 kg), and the patient could only walk with the help of crutches. His height was impossible to estimate (he couldn't stand unaided), and he had knee joint valgity with inflammatory changes in a scar on the right knee joint surface, and ingrowing toenails with inflammatory reaction. Laboratory findings showed i.a. increased serum calcium and *intact* parathormone (*i*PTH) levels (14.48 mg/dl, N. 8.8–10.6 mg/dl and 880 pg/ml, N. 10–73pg/ml, respectively). The first serum phosphorus level was above the referral range, whereas the controlled was decreased (7.53 mg/dl and 1.42 mg/dl respectively, N. 4.0–7.0 mg/dl). All the patient's laboratory investigations are presented in Table I. Features of urinary tract infection were found in urine analysis and confirmed by a bacteriological examination.

Imaging investigations found bone age of 16 years with radiological signs of osteoporosis, but chest X-ray and ultrasound (US) of the abdominal cavity presented no change. In cervical US, a thyroid echostructure non-homogenous with hyperechogenic connective tissue bands was noted. A 99mTc sestamibi (MIBI) scan showed a zone of pathological increased activity in the left thyroid inferior pole and an area of slightly increased activity below the right thyroid lobe reaching the jugular incisure of the sternum. The lumbar (L2-L4) bone mineral density was assessed for 1.061 g/cm^2 in dual-energy X-ray absorptiometry (DXA) and corresponded with a bone age-matched Z-score of –1.15. Diagnostics to exclude cardiological and nephrological reasons for hypertension was performed, and all available data pointed to PHPT as the cause of hypertension. In medical therapy, intravenous liquids with forced diuresis and pamidronate disodium were administrated achieving calcemia, kidney parameters and an improvement in the patient's state.

Concomitantly, a diabetic diet comprising 12 bread units (BU) daily, hypotensive treatment (enalapril, amlodipine), antibiotics (amoxicillin with clavulonic acid, mupirocin) were applied and inflammatory infiltrations around the toenails were evacuated. Finally, correct blood pressure control, body mass reduction to 90 kg, and the regression of coexisting infections were obtained. The patient was referred for surgery. The enlarged (20 × 30 mm) inferior right parathyroid gland and thymus were removed because of adenoma's connection with its superior pole. The result of histopathological examination: *Thymus tissue. Adenoma glandulae parathyreoideae*. On the third day after the operation, normalisation of calcemia was observed. After two months, normal blood pressure without hypotensive treatment was noted, as well as bodyweight of 92.5 kg, correct tolerance of glucose, normocalcemia during requiring calcium and vitamin D_3 supplements (3 000 mg elementary calcium and alfacalcidol 2.5 μg daily), appropriate *i*PTH at decreased $25OHD_3$ and $1.25(OH)_2D_3$ vitamin levels were acquired. DXA densitometry did not present low bone mineral density after 12 months (1.434 g/cm^2) with a bone age-matched Z-score of +2.0.

During follow-up, the patient reached a normal physical efficiency, hypertension and carbohydrate metabolism disorders were not observed. At the age

Table I. *Case no. 1. Results of laboratory investigations at the diagnosis of PHPT*

Tabela I. *Przypadek nr 1. Wyniki badań w chwili rozpoznania pierwotnej nadczynności przytarczyc*

Before surgery	
Leucocytes [G/l]	15.5
Thrombocytes [G/l]	579
Sodium [N. 136–146 mEq/l]	135.5–127.5
Potassium [N. 3.5–5.1 mEq/l]	3.67–3.37
Total calcium [N. 8.8–10.6 mg/dl]	14.48–14.6
Calcium ++ [N. 1.1–1.32 mmol/l]	2.12-2.55
Phosphorus [N. 4.0–7.0 mg/dl]	7.53–1.42
Magnesium [N. 1.8–2.6 mg/dl]	1.69
Urea [mg/dl]	66.9
Creatinine [mg/dl]	1.42–1.69
Endogenous creatinine clearance [ml/min]	108.62 (day)
Endogenous creatinine clearance [ml/min]	98.86 (night)
OGTT: glucose 0'–120' [mg/dl]	90.3–174.4
OGTT: insulin 0'–120' [μIU/ml]	23.7–325.0
Intact PTH [N. 10–73 pg/ml]	880
TSH [N. 0.39–4.62 IU/ml]	0.39
FreeT4 [N. 0.78–2.11 ng/ml]	1.03

OGTT — oral glucose tolerance test

of 18 years and eight months, the patient was 185 cm tall and weighed 82 kg and he was referred to continue control to the Endocrinology Outpatient Clinic of Hollycross Cancer Centre (Świętokrzyskie Centrum Onkologii) in Kielce.

Case no. 2

A girl aged four years four months was admitted for the first time in February 2003 to the Department of PE&D in Kielce with a diagnosis of short stature. History: the child had been born at 39 Hbd of 2nd pregnancy and 2nd delivery with a birthweight of 2,850 g and a length of 51 cm. So far she had been healthy. Her mother was 157.5 cm tall and her father 168 cm. Objectively: height 92.2 cm (under 3rd percentile), weight 11.8 kg (3rd–10th percentile), in examinations — no growth hormone (GH) secretion abnormalities after insulin and clonidine stimulation were found, bone age 36/12 years. Determined total calcium level was normal (9.64 mg/dl, N. 8.8–10.6 mg/dl).

Initially, an idiopathic short stature was recognised, and the patient was recommended for monitoring of growth and body mass. After 20 months, at the age of six years, DXA densitometry was performed because of suspected osteopenia noticed in a wrist joint X-ray. Lumbar (L2–L4) measurements indicated a bone mineral density at level 0.370 g/cm^2, but Z-score was not calculated because of an absence of reference values for a bone age below five years. The result satisfied densitometric criteria of osteoporosis. After 12 months, lumbar (L2-L4) DXA result showed an inappropriately low bone mineral density to gender and age of 0.434g/cm^2 (a bone age-matched Z-score of –2.16). Normocalcemia was observed again (10.12 mg/dl).

Oral calcium and vitamin D_3 were administered as treatment. After 14 months, hypercalcemia (12.36 mg/dl) was noted despite the fact the medicines were not taken. Thus, in January 2007, the child aged 8 years two months was referred for hospital diagnostics due to the suspicion of primary hyperparathyroidism with short stature and body mass deficiency. The follow-up, which lasted for 3 years and 10 months for the diagnosis of PHPT, is presented in Table II. On admission to the hospital, the patient's general condition was good. At the same time, a profile of night GH secretion was performed with results of all GH points under 10 ng/ml, insulin-like growth factor-1 (IGF-1) was appropriate to age and gender. Cervical US found no abnormalities. A 99mTc/MIBI scan indicated areas of pathological increased activity in the left thyroid inferior pole, whereas the subtraction technique found areas of increased activity in both thyroid superior poles and the left side of the isthmus. Clinical and molecular diagnostics were performed which excluded the features of multiple endocrine neoplasia syndrome (MEN) associated with germ line mutation of the *RET* protooncogene. Normocalcemia was achieved due to intravenous liquids and pamidronate administration every month. Finally, the patient was diagnosed with PHPT and referred for surgery. In April 2007, during the neck exploration connected with intraoperative histopathological examination, an enlarged right superior parathyroid gland and a not enlarged

Table II. ***Case no. 2. Summary of patient's follow-up to the diagnosis of PHPT***
Tabela II. ***Przypadek nr 2. Podsumowanie obserwacji dziecka od pierwszego badania do rozpoznania PHPT***

Follow-up	0'	1 year 8 months	2 years 8 months	3 years 10 months
Chronological age	4 4/12	6	7	8 2/12
Height [cm] (percentile)	92.2 (< 3]	103 (< 3]	108 (< 3]	113 (< 3)
Weight [kg] (percentile)	11.8 (3–10]	13.4 (3–10]	14.8 (3–10]	16 (3–10)
Bone age	3 6/12	4 6/12	6 6/12	7
Serum Ca [N. 8.8–10.6 mg/dl]	9.64	10.05	10.12	12.36–12.44
Serum PO4 [N. 4.0–7.0 mg/dl]	(–)	4.25	4.30	3.3–1.94
Urine Ca [N. 1–4 mg/kg/d]	(–)	1.24	4.32	12.9
Urine PO4 [N. 15–20 mg/kg/d]	(–)	20.14	17.43	26.78
Serum Mg [N. 1.8–2.6 mg/dl]	(–)	2.48	2.38	2.07
Urine Mg [N. 2 –3.6 mg/kg/d]	(–)	2.57	3.82	4.48
BMD L2–L4 [g/cm^2]	(–)	0.370	0.434	0.423
Intact PTH [N. 10–69 pg/ml]	(–)	(–)	(–)	112
ALP [N. 69–315 U/l]	(–)	(–)	(–)	257

BMD — bone mineral density; ALP — alkaline phosphatase

right inferior parathyroid gland were removed. The result of histopathological examination: *Superior right parathyroid gland — adenoma glandulae parathyreoideae.* After the surgery, neither severe hypocalcaemia nor "hungry bone syndrome" were observed, and calcium and vitamin D_3 supplements were administered. On the fifth day after the operation, normocalcemia and normophosphatemia were noted. Six months later, serum calcium and phosphorus levels, calciuria and phosphaturia were appropriate during calcium supplementary; lumbar (L2–L4) DXA densitometry indicated BMD at level 0.529 g/cm^2 (a bone age-matched Z-score of –1.46), and *i*PTH was correct. In the tenth year of life there were still no pathological changes of calcium and phosphate metabolism during the treatment of 1,000 mg elementary calcium and alfacalcidol 0.25 μg daily, whereas short stature and body mass deficiency (height under 3rd percentile, weight — 10th percentile) were observed. A decrease of IGF-1 to 34.3 ng/ml (N. to age and gender: 175–445) was presented. The performed diagnostics showed GH secretion deficiency after insulin and clonidine stimulation (GH < 10 ng/ml in all points of the tests). Therefore somatotropic pituitary insufficiency was recognised. In October 2009, the GH therapy was started with a good clinical result. The course of the growth process in this case is set out in Figure 1.

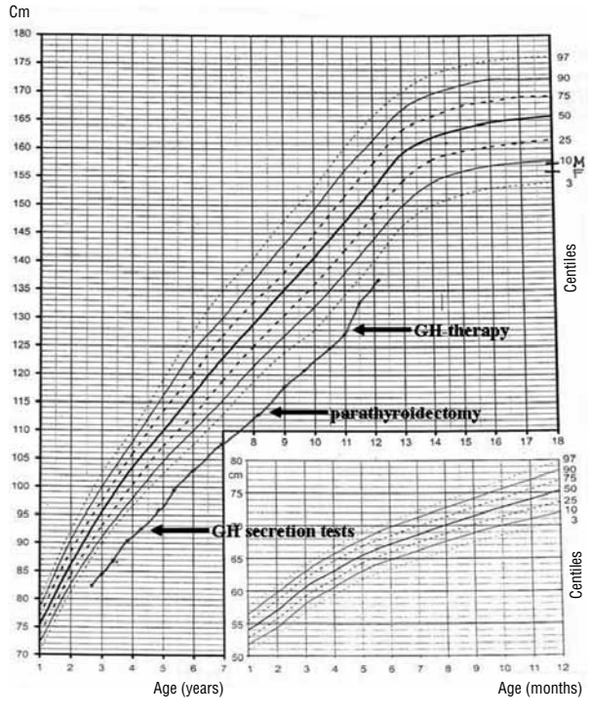

Figure 1. *Growth percentile chart presenting the patient's growing process in Case no. 2*

Rycina 1. *Obserwacja wzrastania dziecka z przypadku nr 2 przedstawiona w siatce centylowej wysokości dziewcząt*

Discussion

Primary hyperparathyroidism occurs rarely in children. In the last decade, only two cases were diagnosed in the Department of PE&D in Kielce. Difficulty in establishing an early diagnosis is due to both non-specific complaints — nausea, abdominal pain, vomiting, fatigue, decreased appetite, weight loss, constipation, osteomuscular pains, learning disability dependent on the development of hypercalcaemia, and the absence of symptoms in the initial phase of the rare occurrence of PHPT in people aged below 18 years. An uncommon measurement of serum calcium in an apparently healthy child or failure it in a diagnostics of long-lasting or rarely acute disorders results in PHPT recognition as an advanced disease [2, 3, 7, 8]. The patient reported in Case no.1 was hospitalised twice within a month before the diagnosis of PHPT, including once because of skeletal disease and the assessment of calcemia was not performed then. It should also be assumed that neurological manifestations inducing hospitalisation were probably the consequence of severe hypertension in the course of an unrecognised hypercalcemic crisis.

Hypertension is not a frequent symptom of PHPT. It occurs in approximately 20–50% of patients, most often with coexisting kidney disorders [9]. Most data in the literature concerns adult observations. The available studies of groups of children and adolescents allow us to regard hypertension as a rather rare symptom of PHPT in this age group — from 0% to 14% [2–4, 10]. Loh et al. [10] suggests that hypertension occurs more often with increasing age: in a group of seven patients aged ≤ 18 years it was recognised in one patient (1/7; 14%), whereas in a group of 15 patients aged 19 to 28 years it was recognised in four patients (4/15; 27%), which corresponds with the prevalence of hypertension found in the adult population. In most reports, the authors agree that children diagnosed with PHPT often suffer from multi-organ damage. At present, nephrolithiasis is known to be a result of increased secretion of PTH in 5–7% of adults [1, 11]. However, in children, nephrological symptoms presenting as renal calculosis have been observed in 33–54%, nephrocalcinosis in 8–16%, and renal failure in single patients [2–6]. In our Case no. 1, renal dysfunction without coexisting nephrolithiasis was observed. Therefore it can be assumed that it was a sign of dehydration in the course of PHPT emergent as a hypercalcemic crisis.

Both in adults and in children, PHPT is rarely recognised in such a life-threatening phase [1, 4, 5]. A classic bone disease with *osteitis fibrosa cystica* is rare, being recognised in less than 10% of adult patients [1]. Therefore, due to the fact that PHPT in

children and adolescents is usually diagnosed late, we should expect advanced bone changes to be common. However, osteopenia, osteoporosis and subperiosteal resorption were the most often encountered skeletal symptoms described in the studies, which emphasised a high percentage of bone changes (16–63% reported by different authors) which confirms late diagnoses of the disease [2–5]. But some authors, such as George et al., found bone pains in 86% of patients, fractures in 60%, and palpable *osteitis fibrosa cystica* in 33.3%, which could possibly result from the geographical and social conditions of the studied group of 15 children with PHPT living in India [12]. Low bone mass features were present in both the cases we describe, but in the girl, although PHPT was early identified, it was more advanced than in the boy, and she was suffering from a severe multi-organ disease.

In our Case no. 1, PHPT and glucose metabolism disorders without pancreatitis were diagnosed concomitantly. Diabetes in PHPT usually appears in the course of pancreatitis as a consequence of hypercalcemia [1, 13]. Recent data suggests the presence of lower insulin sensitivity and hyperinsulinism in adults with PHPT, but significantly higher prevalence of type 2 diabetes mellitus has been documented in older patients (aged 64–75 years) and in men generally [14]. Additionally, a higher calcium level is proposed as an independent predictor of metabolic syndrome and insulin resistance [15]. There is no unequivocal data showing that children and adolescents aged under 18 might present the same correlations. Nevertheless, it would seem to be useful to control glucose and lipid metabolism in the patient reported as Case no. 1 to evaluate cardiovascular risk factors in the future, despite the disappearance of impaired glucose tolerance after successful surgery. In the available literature, growth inhibition in children of post-infantile age with PHPT has not been reported [2–6, 10]. The short stature in our Case no. 2 was an effect of coexisting somatotropic hypopituitarism. Successful surgery of PHPT did not improve the growth, which was not observed only after the introducing to the GH therapy. It is worth noting the early diagnosis of PHPT in this case. The patient was in a good condition with a mild hypercalcemia and symptoms limited to the skeleton at the moment of diagnosis. It confirms our hypothesis of the significant role of calcemia determination as a screening test in the diagnosis of PHPT, including in children.

References

1. Lewiński A, Cyniak-Magierska A. Zaburzenia gospodarki wapniowo-fosforanowej. In: Syrenicz A (ed). Endokrynologia w codziennej praktyce lekarskiej. Wydawnictwo Pomorskiej Akademii Medycznej w Szczecinie. Szczecin 2009; 259–294.
2. Kollars J, Zarroug AE, vanHeerden J et al. Primary hyperparathyroidism in pediatric patients. Pediatrics 2005; 4: 974–980.
3. Lawson ML, Miller SF, Ellis G et al. Primary hyperparathyroidism in a paediatric hospital. QJM 1996; 12: 921–932.
4. Mallet E. Working Group on Calcium Metabolism: Primary hyperparathyroidism in neonates and childhood. The French experience (1984–2004). Horm Res 2008; 3: 180–188.
5. Harman CR, vanHeerden JA, Farley DR et al. Sporadic primary hyperparathyroidism in young patients: a separate disease entity? Arch Surg. 1999; 6: 651–656.
6. 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 (suppl 2): 44–50.
7. Szmit-Domagalska J, Petriczko E, Chrupek M et al. Primary hyperparathyroidism in a 15year-old boy. Endocrinol Ped 2009; 4: 87–94.
8. Kołłątaj W, Szewczyk L. Primary hyperparathyroidism in a 15 year-old boy resembling a chronic gastrointestinal disease. Endocrinol Ped 2008; 1: 81–85.
9. Słowińska-Srzednicka J, Zgliczyński S. Pierwotna nadczynność przytarczyc. In: Januszewicz W, Sznajderman M, Januszewicz A (eds). Nadciśnienie hormonalne. Wydawnictwo Naukowe PWN, Warszawa 1997; 264–267.
10. Loh KC, Duh QY, Shoback D et al. Clinical profile of primary hyperparathyroidism in adolescents and young adults. Clin Endocrinol (Oxf) 1998; 4: 435–443.
11. Shoback D, Marcus R, Bikle D et al. Metabolizm składników mineralnych i choroby metaboliczne kości. In: Greenspan F, Gardner DG (eds). Endokrynologia ogólna i kliniczna. Czelej, Lublin 2004; 296–362.
12. George J, Acharya SV, Bandgar TR et al. Primary hyperparathyroidism in children and adolescents. Indian J Pediatr 2010; 2: 175–178.
13. Dąbrowski A, Jurkowska G, Wereszczyńska-Siemiątkowska U. Choroby trzustki. In: Szczeklik A (ed). Choroby wewnętrzne. Medycyna Praktyczna, Kraków 2005; 857–880.
14. Cardenas MG, Vigil KJ, Talpos GB et al. Prevalence of type 2 diabetes mellitus in patients with primary hyperparathyroisidm. Endocr Pract 2008; 1: 69–75.
15. Luboshitzky R, Chertok-Schaham Y, Lavi I et al. Cardiovascular risk factor in primary hyperparathyroidism. J Endocrinol Invest 2009; 4: 317–321.