Pseudohypoparathyroidism：A Case Report

Pai-Lien Chen, Hsiao-Lien Chen, and Du-An Wu

Division of Endocrinology and Metabolism, Department of Medicine
Lo Tung Poh-Ai Hospital, Lo Tung, Taiwan

Abstract

Pseudohypoparathyroidism (PHP) is a hereditary disorder characterized by symptoms and signs of hypoparathyroidism, typically in association with distinctive skeletal and developmental defects. The hypoparathyroidism is due to a deficient end organ response to parathyroid hormone (PTH). Unlike the patients with idiopathic hypoparathyroidism, the PHP patients had no response to the infusion of parathyroid extract. We describe a 42-year-old woman who has typical features of Albright's hereditary osteodystrophy (AHO), which include a round face, short neck and stature and brachydactyly. Laboratory investigation showed hypocalcemia, hyperphosphatemia with normal PTH level. Brain CT scan revealed calcification at the basal ganglion and cerebellum and hand X ray showed shortening of the fourth metacarpal bone. The patient was diagnosed to have PHP type 1a,on the basis of somatic features of AHO and biochemical abnormalities. (J Intern Med Taiwan 2004; 15: 176-181)

Key Words：Albright's hereditary osteodystrophy (AHO), Pseudohypoparathyroidism (PHP), Pseudopseudohypoparathyroidism (PPHP), parathyroid hormone (PTH)

Introduction

In 1942, Albright reported three hypocalcemic patients with hyperphosphatemia who shared some unusual somatic features and had no response to the infusion of parathyroid extract.

In 1969, shortly after the discovery of cAMP, it was found that the normally brisk increase in urinary cAMP in response to PTH was markedly blunted in PHP, providing a clue that the molecular defects lay in the PTH receptor-adenylyl cyclase complex.

Subsequently, it was shown that many patients with PHP display a 50 percent reduction in the content of the stimulatory G-protein subunit of adenylyl cyclase,

Gs1-2.

Case Report

A 42-year-old woman who was admitted to chest unit firstly due to URI and then referred to our endocrinology service for hypocalcemic problem. This patient was noted to have short stature, round face and obesity (Fig.1). She suffered from frequent attack of muscle cramps. History of regular menstral cycle and menopause occurred since 2 years ago. Her height and body weight were 125.8 cm and 53 Kg , respectively. On physical examination , there were multiple ectopic subcutaneous calcification over the abdomen, both upper and lower extremities with positive Chvostek's and Trousseau's sign. As the patient had typical somatic and skeletal feature of Albright's hereditary osteodystrophy with brachydactyly (short digit) (Fig.2A) and positive signs and symptoms of hypocalcemia, we arranged biochemical test, hand X ray and brain CT scan.

On laboratory investigation, low serum calcium, high serum phosphate levels were noted and serum parathyroid hormone level was within normal limit (Table 1). Twenty four hours urine calcium level was decreased and mild hypothyroidism was also noted. Radiograph of the hands showed marked shortening of fourth metacarpals (Fig.2B). CT scan of the brain revealed intracranial calcification (Fig.3). Further investigation of urinary cAMP response to exogenous PTH infusion test was needed to measure in this patient to differentiate the type of PHP, but PTH preparation is not available at present time and we cannot do this test. However, in this case the hypocalcemia, hyperphosphatemia, normal PTH level, normal renal function with the presence of AHO, favors the diagnosis of PHP type 1a. We treated the patient with vitamin D [calcitriol 0.5 mcg daily] and calcium acetate 667 mg three times per day. Two months later, serum calcium (8.7 mg/dL) and phosphorus (4.0 mg/dL) levels were within normal limit. The associated mild hypothyroidism was treated with sodium levo-thyroxine 50 mcg daily.

Discussion

Pseudohypoparathyroidism (PHP) is a hereditary disorder characterized by symptoms and signs of hypoparathyroidism, typically in association with distinctive skeletal and developmental defects. The symptoms and signs of hypocalcemia develop in childhood. The average age at the onset of symptoms is 8 years, although the diagnosis is not made until adulthood in some relatively asymptomatic persons. As in other hypocalcemic disorders, the presenting symptoms are tetany and seizures 6. Subsequently, PHP patients are prone to the complication of chronic hypocalcemia; calcification of the basal ganglia, which occur in 50 percent; cognitive defects; cataracts; and dental abnormalities, including hypoplasia of dentin or enamel and delay or absence of eruption 6. (Table.2)

Many patients who present with the somatic features, the combination of short stature, brachydactyly, and soft tissue calcification, are distinctive and known as Albright's hereditary osteodystrophy (AHO). Patients are short (usually less than 150 cm), obese and have round faces and short necks. Brachydactyly most commonly affects the fourth and fifth metacarpal bones 6.

PHP presents with hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism. The urinary excretion of calcium may be lower than in hypoparathyroid patients with a similar serum calcium level, and it is not clear whether the renal defect in responsiveness to PTH extends to the distal site of calcium absorption. However, the serum 1α, 25-(OH)2D level is in the low normal range in the face of hyperparathyroidism and hypocalcemia and does not respond normally to the infusion of PTH. The serum level of alkaline phosphatase is normal. The bones may appear to be dense radiographically. In contrast to patients with hypoparathyroidism, PHP patients have evidence of increased bone turn over, with increased urinary excretion of hydroxyproline and reduced bone density and some actually have hyperparathyroid bone disease 3-5.

The classification of the various forms of PHP and pseudopseudohypoparathyroidism (PPHP) is given in Table 3. The classification is based on the signs of ineffective parathyroid hormone action (low calcium and high phosphate), urinary cyclic AMP response to exogenous PTH, the presence or absence of AHO, and assays of the concentration of the Gs subunits of the adenylate cyclase enzyme. Using these criteria, they can be classified into four types: PHP type 1, subdivided into a and b categories; PHP type II; and PPHP 7.

PHP-I is the most common disorder, show a deficient response in urinary cyclic AMP following administration of exogenous parathyroid hormone. PHP type II patients have hypocalcemia, hyperphosphatemia and normal urinary cyclic AMP response to PTH. Patients with PHP-I syndrome are divided into type a, with reduced activity of the stimulatory G protein subunit (Gs) using in vitro assays, and type b, with normal amounts of Gs in erythrocytes. Patients with PPHP have typical features of the hereditary osteodystrophy syndrome despite normal serum calcium and normal response of urinary cyclic AMP to exogenous PTH 7.

The diagnosis can usually be made without difficulty. Positive family history for developmental defects and/or the presence of developmental defects characteristic of PHP-Ia, including brachydactyly, in association with the signs of hypoparathyroidism, low calcium, and high phosphate, essentially make the diagnosis on clinical grounds. PHP-Ib or PHP II has normal phenotype without the AHO syndrome 7.

Although biochemical hypoparathyroidism is the most commonly recognized endocrine deficiency in PHP type 1a, early clinical studies described additional

hormonal abnormalities, such as hypothyroidism and hypogonadism9-11. Primary hypothyroidism occurs in most patients with PHP type 1a. Typically, patients lack a goiter or antithyroid antibodies and have an elevated serum TSH with elevated response to thyrotropin-releasing hormone (TRH). Serum thyroxine (T4) level may be low or low normal. Hypothyroidism may occur early in life prior to the development of hypocalcemia13-15. Reproductive dysfunction occurs commonly in subjects with PHP type 1a. Women may have delayed puberty, oligomenorrhoea, and infertility. Features of hypogonadism may be less obvious in men, but fertility appears to be decreased 11-12.

In our case, the patient who has hypocalcemia, hyperphosphatemia and the typical signs of Albright hereditary osteodystrophy with the normal parathyroid hormone level, favors the diagnosis of PHP type Ia. The long term treatment of hypocalcemia in patients with hypoparathyroidism involves the administration of oral calcium and vitamin D or analogues. Treatment of PHP and PPHP is similar to that of hypoparathyroidism, except that the dose of vitamin D and calcium is usually lower than that required in true hypoparathyroidism 16. The goals of therapy are to maintain the appropriate blood calcium concentration and urinary calcium excretion. In our patient, two months after vitamin D and calcium supplement, the serum calcium and phosphorus level returned to normal limit. We treated with low dose sodium levo-thyroxine daily for the concomitant mild hypothyroid condition.

Conclusion

The elevated serum concentration of PTH in a patient with chronic hypocalcemia, hyperphosphatemia, and normal renal function exclude hypoparathyroidism and suggestive of pseudohypoparathyroidism. PHP is a hereditary disorder, typically manifests a characteristic constallation of developmental defects termed Albright's hereditary osteodystrophy and subcutaneous ossification. Often a definitive diagnosis requires careful examination of radiographs of the hands and feet. Almost all patients with hypoparathyroidism or PHP can be effectively treated with vitamin D in addition to calcium and patients with PHP require lower doses than patients with true hypoparathyroidism.

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Fig.1.Short stature, disproportionate shortening of the limbs, obesity and round face.

Fig.2A.Brachydactyly of the hand, shortening of the fourth digit.
Fig.2B.Radiograph showing marked shortening of the fourth metacarpal.

Fig.3.Brain CT scan showing cerebellum and basal ganglion calcification

Table.1 Laboratory investigation and hormonal profiles

Serum (normal level)	(2002/6)	(2002/11)
Calcium (8.5-10.7 mg/dL)	5.1	8.7
Phosphate (2.5-4.8 mg/dL)	6.1	4.0
Alkaline phosphatase (32-92 U/L)	69.0	
Albumin (3.5-5.0 g/dL)	3.5	
BUN (7.0-22.0 mg/dL)	16.0	
Creatinine (0.6-1.3 mg/dL)	1.4	
Intact PTH (10.0-65.0 pg/mL)	58.7	
FSH (mIU/mL)	19.16	
LH (mIU/mL)	7.81	
E2 (pg/mL)	229.6	
Free T4 (0.78-2.19 ng/dL)	0.56	
TSH (0.465-4.68 μIU/mL)	10.7	
Basal cortisol 8:00am (5-13 μg/dL)	14.69	
ACTH 8:00am (9-52 pg/mL)	40.8	
24 hours urine calcium (110-240 mg/day)	6.3	23.3
24 hours urine protein (<250 mg/day)	325	
24 hours urine phosphate (400-1300 mg/day)		535

Table.2 Symptoms and Signs in Pseudohypoparathyroidism (adapted from reference 6)

Symptom or sign	incidence,%
Somatotype	
Short stature	80
Round face	92
Stocky or obese habitus	50
Mental retardation	75
Dystrophic changes in bone	
Short metacarpals	68
Short metatarsals	43
Calvarial thickening	62
Ectopic ossification	56
Symptoms or signs of hypocalcemia	
Tetany	86
Seizures	59
Cataracts	44
Calcification of basal ganglia	45
Dental abnormalities	55

Table.3 Classification of pseudohypoparathyrodism (PHP) and pseudopseudohypoparathyroidism (PPHP) (adapted from reference 7)

Type	Hypocalcemia, Hyperphosphatemia	Response of urinary cAMP to PTH	Serum PTH	Gs subunit deficiency	AHO	Resistance to hormones in addition to PTH

PHP-Ia	Yes	decreased	increased	Yes	Yes	Yes
PHP-Ib	Yes	decreased	increased	No	No	No
PHP-II	Yes	Normal	increased	No	No	No
PPHP	No	Normal	Normal	Yes	Yes	±

僞性副甲狀腺機能低下症

陳白蓮　陳曉蓮　吳篤安

羅東博愛醫院　內分泌暨新陳代謝科

摘　　要

僞性副甲狀腺機能低下症是一種少見的遺傳性疾病。僞性副甲狀腺機能低下症的特徵，除了副甲狀腺機能低下症的症狀外，典型的骨骼變化與發育不良也有關聯。僞性副甲狀腺機能低下症是因爲副甲狀腺接受器，對於副甲狀腺荷爾蒙反應缺乏引起的。僞性副甲狀腺機能低下症與原發性副甲狀腺機能低下症不同點是對於副甲狀腺荷爾蒙注射完全沒有反應。一位四十二歲的女性患者臨床上有典型的遺傳性骨骼發育不全的表徵，包括圓形臉，粗短的身材與頸部，短指骨等。實驗室檢驗發現低血鈣，高血磷但是副甲狀腺荷爾蒙仍然正常。頭部電腦斷層掃描檢查顯示基底核及小腦有明顯的鈣化點。雙手 X 光檢查發現第四掌骨有明顯的短小。根據病患有典型的外表特徵，骨骼變化及異常的生化檢驗報告，被診斷爲第一型 a 類僞性副甲狀腺機能低下症。因國內少見類似報告故提出此個案加以討論以供參考。