# Albright's hereditary osteodystrophy in conjunction with growth hormone deficiency and adrenal insufficiency

## Albright herediter osteodistrofisi ile birlikte büyüme hormonu eksikliği ve adrenal yetersizlik

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## Abstract

Pseudohypoparathyroidism (PHP) is a rare disease presenting with hypocalcemia, hyperphosphataemia and increased secretion of PTH due to tissue unresponsiveness to the biologic actions of PTH. The term pseudo-pseudohypoparathyroidism (pPHP) is used for patients having the phenotype of Albright's hereditary osteodystrophy (AHO) along with normal biochemical parameters.. The $G_s$ alfa deficiency in PHP Ia may be associated with resistance to TSH or to gonadotropins, resulting in thyroidal and gonadal dysfunction. The female patient presented in this report had all the clinical features of AHO such as a round face, short stature, a short neck, obesity, short of 4$^{th}$ and 5$^{th}$ metacarpals and 4$^{th}$ metatarsal bones symmetrically. PTH level was high, while calcium and phosphorus levels were normal. Her major problem was hypertension resistant to treatment. She was severely obese, her family history for hypertension was strongly positive, but she also had metabolic syndrome. It was speculated that the hypertension was linked to the metabolic syndrome or was associated with the family history rather than be a component of PHP. The patient had both GH deficiency, confirmed by an insulin tolerance test, and adrenal insufficiency. To the best of our knowledge this is the first report of a case of PHP Ia or pPHP in conjunction with both GH and adrenal insufficiency.

**Keywords:** Albright's hereditary osteodystrophy, pseudohypoparathyroidism, growth hormone deficiency, adrenal insufficiency, hypertension

## Özet

Psödohipoparatiroidizm, dokularda PTH duyarsızlığı sonucu hipokalsemi, hiperfosfatemi ve hiperparatiroidi ile seyreden nadir bir hastalıktır. Klinik olarak Albright'ın herediter osteodistrofisi (AHO) fenotipine sahip ama biyokimyasal parametreleri normal olan hastalar ise psödo-psödohipoparatiroidi (pPHP) olarak isimlendirilir. PHP tip Ia'da Gs alfa eksikliği, gonadotropinlere ve TSH'ya direnç ile birlikte görülebilir. Bu yazıda bildirdiğimiz hastada AHO'nun tüm klinik bulguları mevcuttu. PTH düzeyleri yüksek, ancak kalsiyum ve fosfor düzeyleri normaldi. Hastanın esas yakınması tedaviye dirençli hipertansiyondu. Ailede de hipertansiyon öyküsü mevcuttu ve hasta ileri derecede obezdi. Sekonder hipertansiyon açısından yapılan incelemeler de negatif bulundu. Hastada GH eksikliği ve adrenal yetersizlik tespit edildi. Literatürde PHP tip Ia vakalarında gonadotropin, TSH ve GH direnci bildirilmiştir, ancak bu vakalarda ACTH veya kortizol direncine ilişkin yeterli veri bulunmamaktadır. Bu hastamızı, GH eksikliği ve adrenal yetersizlik ile birlikte olan, bir tip Ia PHP vakası olarak bildiriyoruz. Bilgilerimize göre bu, literatürde ilk vakadır.

**Anahtar sözcükler:** Albright'ın herediter osteodistrofi, psödohipoparatiroidizm, büyüme hormonu eksikliği, adrenal yetersizlik, hipertansiyon

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## Introduction

Pseudohypoparathyroidism (PHP) is a rare disease that presents with hypocalcemia, hyperphosphataemia and increased secretion of PTH because of tissue unresponsiveness to the biologic actions of PTH. In addition to hypoparathyroidism, many patients with PHP exhibit developmental and skeletal defects which are collectively termed *Albright's hereditary osteodystrophy* (AHO). The characteristics of AHO include a round face, a short and stocky stature, brachydactyly, heterotropic ossification and mental retardation. If the affected individuals have AHO without evidence of any endocrine dysfunction, this disease is named as pseudo-pseudohypoparathyroidism (pPHP)[1]. The major problem in all types of PHP is an inactivating gene mutation in *GNAS1* gene which leads to a deficiency of calcium-sensing receptors and of Gs alfa protein. However, *GNAS1* inactivating mutations may not be present in all types of PHP (Figure 1).

Reproductive dysfunction, including delayed puberty, oligomenorrhea and infertility, occur more commonly in subjects with PHP type Ia[2,3]. Plasma gonadotropins may be elevated in these patients. Obesity is common in PHP Ia and pPHP patients[4,5]. Presence of obesity reflects defective lipolytic response to hormonal stimulation. Due to tissue resistance to several hormones, antibody negative-primary hypothyroidism is also encountered in most patients with PHP Ia[2]. Recent studies of pituitary function in subjects with PHP type Ia have demonstrated that GH deficiency occurs in about 70%[6,7].

The idiopathic and inherited forms of PTH resistance were first described by Albright in 1942[8]. These patients were hypocalcemic and hyperphosphataemic and also had some of the clinical features of the entity called Albright's Hereditary Osteodystrophy (AHO) such as short stature, rounded face, brachydactyly, obesity and subcutaneous calcifications[9].

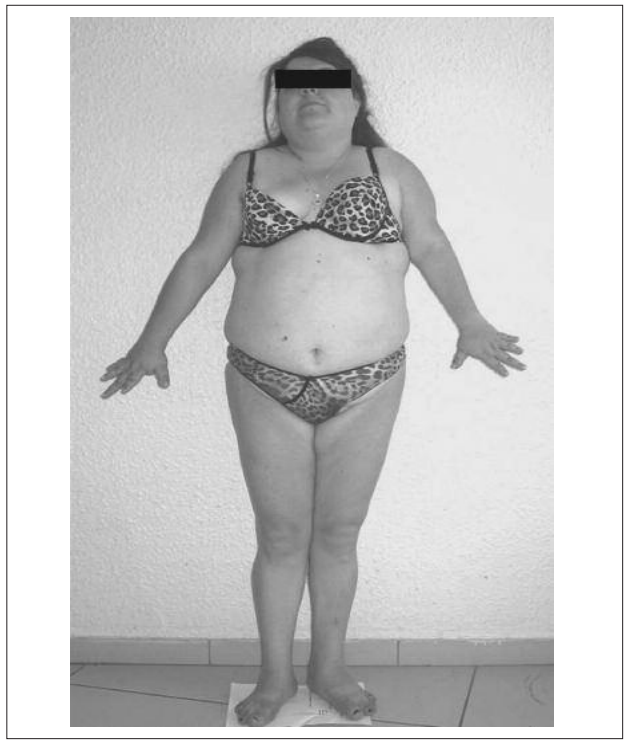

**Fig 1.** The characteristics of AHO were significant in our patient and included round face, short neck and stature, abdominal obesity, stocky physique and brachydactyly

Hypocalcemic patients with AHO have elevated PTH levels and PTH infusions fail to stimulate renal production of cAMP or increase in serum calcium. The measurement of urine cAMP level following synthetic PTH infusion is now used to establish the diagnosis of PTH resistance[10].

The variable presence of AHO and renal PTH resistance has led to the subclassification of pseudohypoparathyroidism (PHP). Subclassifications and characteristics of PHP and differentiation from pPHP are summarized in Table 1[1,9]. The Gs alfa deficiency in

**Table 1:** Characteristics of subgroups of PHP Type I and and their differentiation from pPHP and PHP Type II

| | PHP Ia | PHP Ib | PHP Ic | pPHP | PHP |
|---|---|---|---|---|---|
| IIPhysical appearance(AHO) | (+) | (-) | (+) | (+) | (-) |
| Urinary cAMP response to PTH | ➤ | ➤ | ➤ | N | N |
| Urinary PO4 response to PTH | ➤ | ➤ | ➤ | N | ➤ |
| Serum Ca level | ➤ / N | ➤ | ➤ | N | ➤ |
| Resistance to other hormones | (+) | (-) | (+) | (-) | (-) |
| Pathophysiology | $G_s$alfa activity reduced | $G_s$alfa activity normal | $G_s$alfa activity normal | $G_s$alfa activity reduced | Vitamin D myotonic dystrophy |

PHP Ia may be associated with resistance to TSH, glucagon or gonadotropins, resulting in thyroidal and gonadal dysfunction. In PHP Ib, patients present with hypocalcemia and hyperparathyroidism, without showing any of the clinical features of AHO. The only consistent feature of PHP Ib is renal resistance to PTH. It is caused by defects in GNAS 1 gene (20q13.3) encoding $G_s$ alfa[11]. Patients who show the features of AHO with PTH resistance and normal $G_s$ alfa activity have been classified as PHP Ic.

In PHP II, the only abnormality is a decreased urinary PO4 response to PTH infusion. This rare syndrome is not familial and the patients can present at ages ranging from infancy to adulthood.

Patients with the phenotype of AHO but with normal biochemical parameters are called pseudo-PHP (pPHP). When these patients inherit the mutant gene from their father, they exhibit the features of pPHP while features of PHP develop if the gene is inherited from the mother[12,13]. This pattern is termed "genetic imprinting"[14].

## Case report

We report a 38-year old female patient who presented with hypertension resistant to treatment, with complaints of severe headache and nausea. The patient reported that she was taking anti-hypertensive medicines (Cilazapril 5 mg/d + Hydrochlorothiazid 12.5 mg/d + Atenolol 50 mg/d) and had been on thyroid hormone replacement therapy (150 µg/d) for 3 years. At admission the patient's blood pressure (BP) was 240/180 mmHg. She did not have chest pain or any visual defect. She said that she was not feeling well and reported that she had episodes of tachycardia triggered by emotional stress. During these episodes, she usually checked her blood pressure and found very high levels (systolic BP above 200 mmHg). She denied having flushes or orthostatic hypotension during hypertensive periods. There was no history of dysuria, nocturia, hematuria or any volume change in the urine.

The patient reported that she had her first menstrual cycle when she was 16 and that her cycles had always been irregular. She had started to gain weight and had increased body hair since she was 19. The patient's history also revealed that both her parents and her grandmother had hypertension and her brother had primary hypothyroidism. Hpwever, no one in her family had similar clinical features.

On physical examination, she had short stature, a round face, a short neck, obesity, short limbs and fingers. BMI was calculated as 35.6 kg/m$^2$, BP was 150/90 mmHg, pulse was 62/min. Thyroid gland was bilaterally palpable. Expiration was minimally prolonged. There was a 2/60 systolic murmur on cardiac examination. Abdominal examination showed no organomegaly or abnormality. The Ferriman-Gallway score was 6.

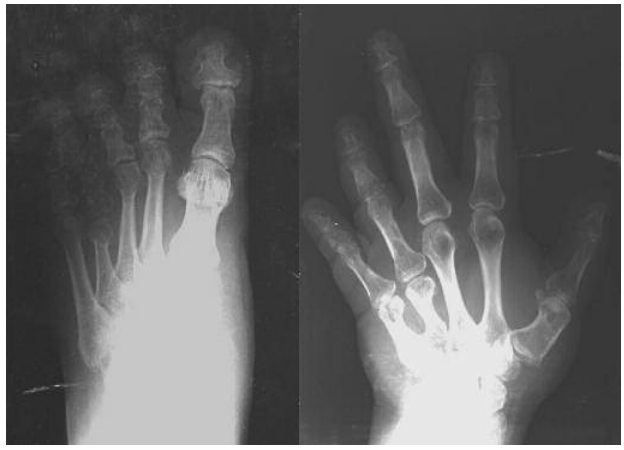

**Fig 2.** X-ray showing short 4th and 5th metacarpals and short 4th metatarsal

The patient had been hospitalized in another hospital in March 2005, because of uncontrolled hypertension. The abdominal MR angiography performed in that hospital was reported as normal but a grade 2 hepatosteatosis had been detected on abdominal ultrasound. Her laboratory findings at this previous hospitalization had revealed high triglycerides levels (1376 mg/dL; normal ranges 30-200 mg/dL) high LDL levels (275 mg/dL; normal ranges 0-140 mg/dl) and high total cholesterol levels (435 mg/dL; normal ranges 30-200 mg/dL).

Laboratory investigations performed in our clinic showed a TSH level of 9.6 uIU/mL an (0.27-4.2 uIU/mL), anti-tyroglobulin antibody level of 51.1 IU/mL and thyroid peroxidase antibody level of 521 IU/mL, We decided that the patient had Hashimoto's thyroiditis and that the dose of thyroid hormone she was receiving was not adequate and we increased the dose to 200 µg/d. Blood calcium, phosphorus, magnesium and alkaline phosphatase (ALP) levels were in normal ranges while PTH was high by our laboratory standards (79.9 pg/mL; normal ranges 10-67 pg/mL). FSH, LH, E2, progesterone, testosteron, ACTH and cortisol levels were all within normal ranges. GH was <0.05 ng/mL and IGF1 was 84.4 U/mL which was low for her age (normal range appropriate for age is 101-284).

Pelvic and abdominal ultrasound examinations were reported as normal. The gynecologic examination performed by a gynecologist was normal. On hand and foot radiographs symmetrical shortness of the 4t$^h$ and 5$^{th}$ metacarpals and of the 4$^{th}$ metatarsal bone were noted. These findings led us to consider a diagnosis of Albright's hereditary osteodystrophy (Figure 2).

A 24 hour urine VMA and metanephrines assessment was done to distinguish the hypertension from endocrine hypertension. This analysis was repeated 3 times and all samples were reported to show normal ranges (VMA 2.2 mg/d, Metanephrine 29 ug/d). Serum 25 (OH) D3 and 1.25 $(OH)_2$ D3 levels were determined to exclude the possibility of a secondary hyperparathyroidism due to hypovitaminosis D. Both 25 (OH) D3 and 1.25 $(OH)_2$ D3 levels were low (25-OH-D3 was 20ng/mL; normal ranges 10-40 ng/mL and 1.25-OH-D3 was 20 pg/mL; normal ranges 30-65pg/mL), so the patient was started on vitamin D3 replacement therapy

The patient's GH level was <0.05 ng/mL, her IGF-1 level was also low. Her basal cortisol level was 8 ug/dL, which is also a level in the lower range of normal. An insulin tolerance test (ITT) was also performed. The results of ITT showed GH deficiency and also showed that the cortisol level had not increased adequately during hypoglycemia (maximum level was 13 ug/dL). However, the patient did not have any clinical findings consistent with adrenal insufficiency.

The patient's blood pressure was brought under control with a combination therapy (Atenolol 50 mg/d + Ramipril 5 mg/d + Amlodipin 10 mg/d + Doxazosin mesylate 8 mg/d). We also prescribed phenofibrate for hypertriglyceridemia.

Pseudohypoparathyroidism type 1b was excluded by mutation analysis of GNAS. After 6 months, the PTH level increased to 167 pg/mL. ALP level was found to be elevated in spite of taking vitamin D replacement therapy. Calcium and phosphorus levels continued to be in normal ranges.

## Discussion

Our patient showed all the clinical features of AHO such as a round face, short stature, a short neck, obesity, short $4^{th}$ and $5^{th}$ metacarpals and short $4^{th}$ metatarsal bones. PTH level was high while calcium and phosphorus levels were normal.

Pseudohypoparathyroidism type 1b was excluded by investigation of exons 2-13 of *GNAS*, but analysis of Gs alfa activity could not done. Normal Ca and P levels along with increased PTH levels and with features of AHO were initially thought to be suggestive of pPHP. However, the fact that PTH levels continued to increase despite vitamin D replacement therapy and also the findings indicating resistance to other hormones (hypothyroidism, delayed puberty, oligomenorrhea, GH deficiency and partial adrenal insufficiency) led us to consider PHP type Ia as the diagnosis. While elevated PTH levels can be detected early in some cases, Ca and P levels may be normal. Changes in Ca and P levels may appear slowly over tine or no decrease in calcium may be detected due to normal Gs alfa activity. Furthermore, clinical features resulting from resistance to other hormones (like hypothyroidism, delayed puberty) are usually more prominent in paients with PHP type Ia[15] Izraeli et al have reported 5 such cases from a family, where Gs alfa activity was normal although features of AHO and hypothyroidism were present. This suggests that mutations in different regions may result in different presentations of the disease. Although PHP is an inherited disease, there were no other individuals who had the same disease or its clinical features among the members of our patient's family. This may be because PHP and pPHP are genetically heterogeneous diseases.

Idiopathic GH deficiency associated with pPHP was previously reported by Manfredi et al[16]. Our patient had GH deficiency and partial adrenal insufficiency although she did not show have any related clinical symptoms. Although hypoadrenalism is not a typical feature of PHP Ia, there are 2 cases of adrenal insufficiency associated with AHO reported in the literature[17,18]. To our knowledge, our patient is the first reported case who had both adrenal insufficiency and GH deficiency associated with PHP Ia.

Oligomenorrhea and hypothyroidism were also clinical features present in this patient. She gave a history of delayed puberty and oligomenorrhea which are commonly encountered in PHP Ia. The patient was single and had not desired pregnancy, so we did not analyze more extensively for infertility.

The major problem in our patient was uncontrolled hypertension. Her blood pressure was still high despite using a combination of three anti-hypertensive drugs. Association of PHP with arterial hypertension has been previously reported. Brickman et al.[19] reported that high blood pressure was strongly related to severe obesity in 46 patients with PHP Ia and Ib. Circadian variation of catecholamines and blood pressure have been investigated in hypertensive patients with PHP, and the correlation of mean arterial blood pressure with plasma nor-epinephrine was found to be weaker as compared to that found in patients with essential hypertension. The same researchers reported that the variability and concentrations of plasma renin activity (PRA) and aldosterone over 24 hr were considerably lower in PHP patients[20]. These studies also suggested that hypertension may be associated with severe obesity in these patients. Also, in our patient, family history of hypertension was very strong, a finding which was suggestive of essential hypertension. The patient also showed all features of the metabolic syndrome (a fasting blood glucose of 112 mg/dL, Tg>150 mg/dL, waist circumference >88 cm), thus the hypertensive state could also have developed as a component of the metabolic syndrome.

In conclusion, we report this patient as a rare case having both GH deficiency and adrenal insufficiency ac-

companying Albright's hereditary osteodystrophy. She also had primary hypothyroidism and reproductive dysfunction. This patient represents a case of multiple hormone resistance caused by Gs alfa inactivation in several tissues, a condition which is more typical for PHP Ia. The patiemt had resistant arterial hypertension along with severe obesity and insulin resistance and a strongly positive family history for hypertension. It is possible that the hypertension in this patient may have developed as a component of the metabolic syndrome or may be due to essential hypertension, instead of being associated with pseudohypoparathyroidism.

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