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NORMOKALSEMiK SEYREDEN PSÖDOHiPOPARATiROiDİZM TİP I A

ÖZET:

Psödohipoparatiroidizm (PHP); parathormon hedef organ direnci olan, hipokalsemi, hiperfosfatemi ve kan parathormon (PTH) yüksekliği ile karakterize heterojen bir hastalık grubudur. Albright'ın herediter osteodistrofisi olarak da adlandırılan tip Ia'da tipik fenotipik bulgular ve ek hormon dirençleri de görülebilmektedir. Kısa boy, obezite, yuvarlak yüz, basık burun kökü, kısa metakarplar ve hafif mental retardasyon gibi Albright'ın herediter osteodistrofisinin tipik bulguları olan kız hastamız 8 yıl 9 aylık idi. Biokimyasal tetkiklerinde normal kalsiyum ve fosfor düzeylerine rağmen yükselmiş PTH düzeyi ve hipotiroidizm saptandı. Hastanın klinik ve laboratuvar bulguları normokalsemik seyreden PHP tip Ia ile uyumlu bulundu. Guanin bağlayıcı protein (G protein), alfa subunit 1 (GNAS 1) geni dizi analizi sonucunda daha önce PHP tip Ia'lı olguda bildirilen C-308T>C(p1103T) değişimi saptandı. Burada PHP tip Ia'da kan kalsiyum ve fosfor düzeylerinin normal saptanabileceğini vurgulamak istedik.

Anahtar Sözcükler: Psödohipoparatiroidizm, Albright herediter osteodistrofisi, Normokalsemi, Kısa boy

PSEUDOHYPOPARATHYROIDISM TYPE I A WITH NORMOCALCEMIA

Abstract:

Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorder with parathormone target organ resistance, characterized by hypocalcemia, hyperphosphatemia and high blood parathormone (PTH). Typical phenotypic symptoms and additional hormonal resistance can be observed in type Ia, which is also known as Albright hereditary osteodystrophy. Our patient was an eight-year and nine-month old girl with typical Albright's hereditary osteodystrophy phenotype including short stature, obesity, round face, low nasal bridge, shortened metacarpals, and mild mental retardation. In her biochemical examination, high PTH level and hypothyroidism is detected in spite of normal calcium and phosphor levels. As a result of clinic and laboratory tests, the findings were consistent with PHP type Ia with normocalcemia. In her guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1 *(GNAS 1)* gene serial analysis, C-308T>C (p1103T) transformation was detected, which was previously reported in a PHP type Ia patient. In this report, we've aimed to emphasize the fact that calcium and phosphor level in the blood of the patient with PHP type Ia can be measured normal.

KEYWORDS: Pseudohypoparathyroidism, Albright hereditary osteodystrophy, Normocalcemia, Short stature

INTRODUCTION

Pseudohypoparathyroidism (PHP) is an autosomal dominant disorder, which occurs with parathormone target organ resistance resulting from guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1 **(***GNAS1*) gene mutation. It is characterized by hypocalcemia, hyperphosphatemia and elevated PTH levels (1). The disorder occurs as a result of maternal transmission of the mutation. As Gs alpha protein activity is necessary for other hormones such as thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH), the resistances against these hormones may also exist (6,7,9,11,13). Characteristic phenotypic features such as short stature, obesity, round face, low nasal bridge, shortened metacarpals, shortness and thickness in distal phalanges, subcutaneous calcifications, polyostotic fibrous dysplasia, developmental delay, and besides, mental retardation can be observed in these patients (1, 8). This phenotype is named as Albright hereditary osteodystrophy (AHO).

Some cases with PHP type Ia are present with heterogeneity in terms of their phenotypical and biochemical characteristics (10,12,14,15). In this paper, an eight-year and nine-month old female case with normocalsemic PHP type Ia is reported.

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CASE REPORT

Eight-year and nine-month old female patient was admitted to the hospital with the complaint of short stature presented with a height of 117.2cm (<3p, -2.5 SDS) and weight of 28.9 kg (50-75p, 0.124 SDS). Term, birth weight and birth height were 3100 gr (25-50 p) and 50 cm (50-75 p) respectively. Her parents was third-degree relatives. The father's and mother's heights were 165 cm (-1.65 SDS), and 135.9 cm (-4.2 SDS) respectively. She had healthy four siblings. Her physical examination at presentation showed a short stature, obesity, round face, low nasal bridge, and shortened metacarpals (picture 1 and 2). Her pubertal stage was in tanner phase 1. She was evaluated as mentally retarded in a mild degree.

Skeletal maturation assessment by direct hand wrist radiography revealed shortened metacarpals and metatarsals (picture 3) and her bone age was consistent with her age. Her thyroid ultrasonography and cranial magnetic resonance imaging were both reported as normal. Hypothyroidism and elevated PTH levels with normocalcemia and normal 25 OH vitamin D levels were detected in her laboratory tests. Laboratory findings results including complete blood counts, biochemical parameters, TSH, free T4, calcium, phosphorus, alkaline phosphatase PTH level 25-hydroxyvitamin D insulin like growth factor 1(IGF-1) were given in table 1.

As a result of clinic and laboratory tests, the findings were consistent with PHP type Ia with hypotyroidism and normocalcemia, her GNAS gene sequencing analysis was performed; C-308T>C (p1103T) transformation was detected, which was previously reported in PHP type Ia patient. Oral L-thyroxine treatment was initiated to the patient. Her growth velocity and calcium and phosphorus levels are still on follow-up.

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DISCUSSION

Pseudohypoparatyroidism Ia is the most prevalent PHP type. Along with typical phenotypic findings, cases showing heterogenity have also been reported (16-18). Our patient had typical AHO phenotypes.

Transport system which is sensitive to parathormone consists of three sections namely receptor, adenyl cyclase and protein G. The GNAS gene encodes the alpha-stimulatory subunit (Gs) of the intracellular G protein, which stimulates the production of cAMP under certain physiologic conditions (8). Gs alpha protein activity in PHP-Ia is low as a result of GNAS 1 gene mutation therefore, sufficient c-AMP response to PTH cannot occur in receptor level (2-5). Resistance to other hormones which use protein G as a second messenger, may also be observed. Moreover, the most common resistance is observed against TSH, which affects more than 90% of PHP type Ia patients (19, 20). Previous reports have shown hypothyroidism may be the first manifestation of PHP type Ia in absence of hypocalcemia and elevated PTH levels (10-21). In our case, hypothyroidism with elevated TSH and decreased sT4 levels is detected.

The characteristic findings of the disorder are hypocalcemia, hyperphosphatemia and high level of PTH. However, previously normocalcemic cases have also been reported (14, 22-24). Tamada et al. reported a case with R358H mutation with normocalcemia (24). We have detected C-308T >C (p1103T) change in our case. The mechanism behind the fact of normocalcemia cannot be explained completely. It is proposed that normal serum calcium concentrations in these patients may be explained by the presence of normal bone responsiveness to PTH (14, 25, 26). Further studies are needed on this issue.

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In conclusion, we have presented a PHP type Ia patient with normocalcemia and hypothyroidism caused by C-308T >C (p1103T) change in the GNAS gene. In children with hypothyroidism without apparent etiology, GNAS1 gene mutations should be also considered even calcium levels are normal.

Table 1.

Hemoglobin (g/dl)*	12.9 (11 - 13)**	ALT (U/L)	15 (8.7 – 39)
MCV (fL)	85.6 (75 – 90)	AST (U/L)	192 (100 – 500)
Platelet (10*3 u/L)	227 (142 – 424)	fT4 (pmol/L)	8.71 (11.2 – 18.6)
Leucocyte (10*3 u/L)	7.2 (6 – 17)	TSH (mIU/L)	9.2 (0.51-4.82)
Sodium (mmol/L)	140 (139 – 146)	Calcium (mg/dl)	9.7 (8.8-10.8)
Potassium (mmol/L)	4.4 (4.1 – 5.3)	Phosphorus (mg/dl)	5.8 (3.78-6.19)
Chlorine (mmol/L)	105 (98 –106)	ALP (U/L)	205 (135-537)
BUN (mg/dl)	12.5 (5.1 – 16.8)	PTH (pg/ml)	436.9 (15-68.3)
Creatine (mg/dl)	0.44 (0.35 – 0.59)	25 OH vit D (ng/ml)	28 (20-70)
Fasting Glucose (mg/dl)	80 (50-80)	IGF-1 (ng/ml)	197 (51-303)

MCV: mean cell volume, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, fT4: free tetraiodothyronine, TSH: thyroid stimulating hormone ALP: alkaline phosphatase, IGF-1: insuline like growth factor-1
*Laboratory measurement units; **Reference Values

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Written informed consent was obtained from the patient's parents for publication of this case report.

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Şekil 1

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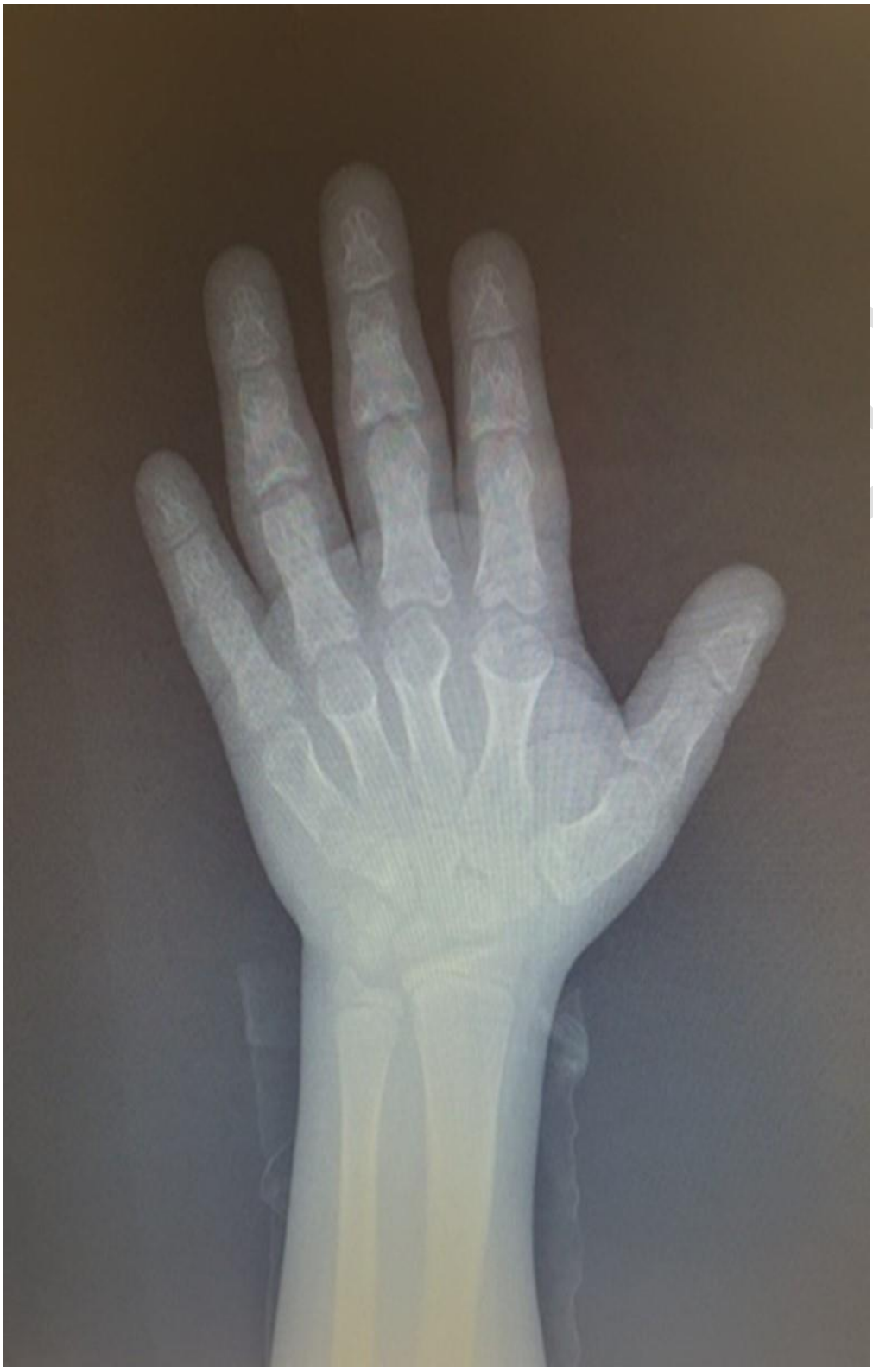

Şekil 3

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