

EDİTÖRE MEKTUP / LETTER TO THE EDITOR

A rare cause of hypocalcemia: pseudohypoparathyroidism

Nadir bir hipokalsemi nedeni: psödohipoparatiroidizm

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To the Editor,

Pseudohypoparathyroidism (PHP) is a rare disease with genetic inheritance; its prevalence is estimated to be about 0.79 per 100.000¹. PHP was described for the first time in 1942 by Albright et al² and there are 5 types of pseudohypoparathyroidism: PHP type 1a, type 1b type 1c, type 2 and pseudopseudohypoparathyroidism. PHP type 1a is the most common subtype and represents 70% of the cases³. PHP-1 is characterized by the Albright's hereditary osteodystrophy (AHO) phenotype (round face, short stature, subcutaneous ossifications, brachydactyly, and early-onset obesity) and parathyroid hormone (PTH) resistance^{4,5}. PTH resistance is manifested by hypocalcemia, hyperphosphatemia and elevated circulating PTH¹. The gene that causes the disease is GNAS, which encodes the alpha subunit of the stimulating G protein (G α)⁶. Along with the PTH resistance, PHP-1a patients may also be resistant to hormones that work with Gs-linked receptors such as TSH (thyroid-stimulating hormone), FSH(Follicle-stimulating hormone), LH(Luteinizing hormone), and GHRH(Growth hormone-releasing hormone)¹. Here, we present a patient with pseudohypoparathyroidism which is a rare cause of hypocalcemia and PTH resistance.

A 34-year-old female patient presented with complaints of contractions in the whole body, muscle weakness and loss of appetite. She stated that these complaints have been going on for 10 years. She has been amenorrheic since at the age of 22. The patient had secondary amenorrhea. On physical examination,

she had phenotypic features of AHO such as obesity, short neck, short height, round face, shortness and thickness in the hand bones (Figure 1).



Figure 1. Clinical features of patient.

In biochemical examination, hemogram, urea, creatinine, aspartate aminotransferase (AST), Alanine aminotransferase (ALT), albumin, and magnesium levels were normal other laboratory results demonstrated in table 1.

Table 1. Laboratory results

	Patient values	Normal reference range
Calcium (mg / dl)	5.8	8.8-10.2
Phosphorus (pg / ml)	5.6	2.7-4.5
PTH (pg / ml)	267	15-65
25-OH vit D (ng / ml)	33	4.92-42.7
TSH (mIU/L)	5.7	0.27- 4.2
fT4 (ng / dl)	0.65	0.6-1.2
FSH (mIU/ml)	7.9	3.6- 12.6
LH (mIU/ml)	8.3	2.4-12.5
Testosterone (ng / ml)	0.12	0.14-0.76
Estradiol	49.2	12.4-166

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone; TSH: thyroid-stimulating hormone;

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Fourth and third metacarpal shortness was noted on hand radiographs (Figure 2). Widespread calcifications were detected in the basal ganglia and bilateral hemispheres in cranial CT. Calcium gluconate infusion, synthetic calcitriol for hypocalcemia, L-thyroxine for hypothyroidism and estradiol + progesterone for secondary amenorrhea were started. The patient was diagnosed with PHP with the present physical examination findings and laboratory features.



Figure 2. Radiography of hands

Sample was taken for genetic examination and the result was concluded in accordance with the prediction. Somatic mutation was detected in the GNAS gene that caused the disease. The patient whose calcium level reached normal limits is still under follow-up.

Gs α -coding GNAS mutations that lead to diminished Gs α expression and/or function result in Albright's hereditary osteodystrophy (AHO) with or without hormone resistance, i.e. pseudohypoparathyroidism type 1a/1c and pseudo-pseudohypoparathyroidism, respectively. Mutations of GNAS that cause constitutive Gs α signaling are found in patients with McCune-Albright syndrome, fibrous dysplasia of bone, and different endocrine and non-endocrine tumors⁷. Parathyroid hormone (PTH) is significant hormone which plays role in the regulation of serum calcium via the Gs-coupled receptor⁸. PHP is a clinical syndrome that characterized by target organ resistance to the hormone. The defect in the Gs-coupled receptor is responsible for this resistance. These patients also have other hormone deficiencies using the same receptor. Other than hypocalcemia and hyperphosphatemia, pathologies such as hypothyroidism and hypogonadism can be detected⁹.

In this case, hypothyroidism and hypogonadism were present due to multiple hormone resistance.

Chronic hypocalcemia with hyperphosphatemia may cause ectopic calcification¹⁰. Although calcifications were detected in the basal ganglia and bilateral hemispheres in cranial CT in our case, we did not find any pathological findings in neurological examination. Treatment of severe hypocalcemia is not different from other forms of hypoparathyroidism and should target calcium and phosphorus levels in the normal range with oral forms of calcium and active vitamin D¹⁰. Due to severe hypocalcemia, we targeted normal calcium level with intravenous calcium replacement in our case, and then proceeded with oral calcium and activated forms of vitamin D replacement.

In patients with characteristic phenotypic appearance accompanying hypoparathyroidism, Albright's osteodystrophy should be considered in the differential diagnosis and also evaluation should be done in terms of thyroid and gonadotropin hormone resistance.

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