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Case Report

Delayed diagnosis of pseudohypoparathyroidism type 1a with rare hypothyroidism since childhood

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Abstract

Pseudohypoparathyroidism (PHP) is a rare disorder that associates with resistance to parathyroid hormone (PTH). A 21-year old man visited outpatient clinic to treat previously diagnosed hypothyroidism and vitamin D deficiency. Despite daily 150 mcg of levothyroxine supplement, thyroid-stimulating hormone level was elevated, but thyroid autoantibodies were not detected. He showed features of Albright Hereditary Osteodystrophy and elevated serum PTH level with normal albumin-corrected calcium and phosphorus level. The Ellsworth-Howard test proved the blunted response of urinary phosphorus and cyclic adenosine monophosphate after the infusion of the exogenous PTH, suggesting PTH resistance. DNA analysis revealed a heterozygous mutation in the *GNAS* gene (c.478C > T). Herein, we report a case of PHP type 1a confirmed by clinical, biochemical and molecular analyses. Establishing correct diagnosis of PHP is necessary for efficient therapeutic management.

INTRODUCTION

Pseudohypoparathyroidism (PHP) is a rare disorder that shares the biochemical features of hypoparathyroidism such as hypocalcemia and hyperphosphatemia, owing to the resistance of target tissue to the biological actions of parathyroid hormone (PTH) [1]. PHP consists of five variants, namely 1a, 1b, 1c, 2 and pseudopseudohypoparathyroidism—which are based on pathogenesis and phenotype [1]. PHP type 1a is characterized by a group of physical features known as Albright Hereditary Osteodystrophy (AHO) that includes short stature, obesity, a round face, brachydactyly and ectopic ossifications [1, 2]. We report on an adult patient with PHP type 1a who had an unusual presentation of primary hypothyroidism since childhood.

Case report

Hypothyroidism and vitamin D deficiency had been diagnosed in our 21-year-old male patient when he was 9 years old because of his stunted growth. Physical examination found short stature (154.7 cm; normal range > 160), overweight (body mass index of 25.3 kg/m^2; normal range = 18.5–24.9) and a round face, even as an adult (Fig. 1). His teeth were pigmented, suggestive of enamel hypoplasia, and brachydactyly, with short metacarpals and metatarsals (Fig. 2**a**), were observed. His sexual maturity rating was Tanner stage 5, and he did not have any psychomotor symptoms. Radiographs revealed short fourth and fifth metacarpals and metatarsals on both hands and feet (Fig. 2**b**). Bone mineral density was normal. Computed tomography showed no sign of brain calcinosis.

Figure 1. Albright hereditary osteodystrophy features of our patient (short stature, overweight and a round face).

Laboratory results showed normal albumin-corrected calcium and phosphorus, elevated serum PTH (101.6 pg/ml; normal range = 15.0–65.0), normal 25-hydroxyvita

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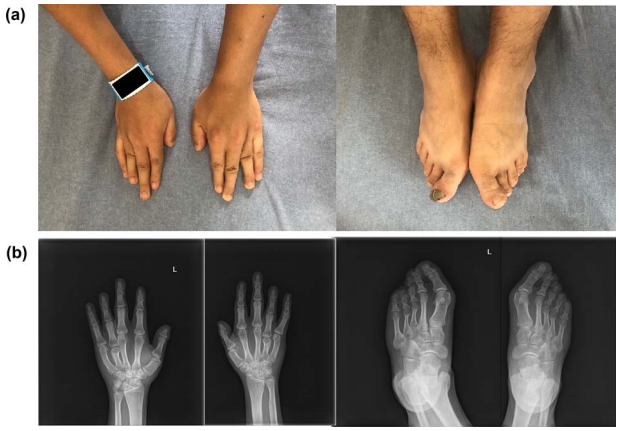

Figure 2. Brachydactyly with short metacarpals and metatarsals.

min D (25.5 ng/dL; normal range = 10.0–30.0) and normal estimated glomerular filtration rate (100 ml/min/1.73m^2; normal range > 60). Among bone turnover markers, serum C-terminal telopeptide of type 1 collagen was slightly elevated (0.94 ng/ml; normal range = 0.016–0.584), whereas osteocalcin and bone-specific alkaline phosphatase levels were normal. The patient had an elevated thyroid-stimulating hormone (TSH) level (6.5 μIU/ml; normal range = 0.35–4.94) from taking 150 mcg of levothyroxine, but had no goiter or thyroid autoantibodies. He had a slightly elevated prolactin level (23.7 ng/ml; normal range = 4.1–18.4), but normal levels of free T4, follicle-stimulating hormone, luteinizing hormone, serum testosterone, adrenocorticotropin, cortisol, IGF-1 and growth hormone (Table S1). Finally, we used the Ellsworth-Howard test to determine the PHP type (Fig. 3). The responses of urinary phosphorus and cyclic adenosine monophosphate (cAMP) were markedly attenuated after the infusion of the exogenous PTH (40 μg; teriparatide; IN, USA) as previously described [3].

The patient received a diagnosis of PHP type 1a based on finding of hypocalcemia with hyperphosphatemia, his AHO features, PTH resistance and possible TSH resistance. To support the diagnosis, we performed DNA analysis of the guanine nucleotide (GTP)-binding α-subunit gene (*GNAS*). Sequencing of the amplified genomic DNA fragments of *GNAS* detected a heterozygous missense mutation within exon 6 (c.478C > T) [4].

Active vitamin D metabolites with calcium carbonate were administered and the levothyroxine was maintained. After 18 months of treatment, his PTH level had decreased to within the normal range (59.1 pg/ml; normal range = 15.0–65.0) with normocalcemia. Thyroid function tests, including a TSH level, were also normal.

DISCUSSION

PHP type 1a is an uncommon genetic disorder characterized by the association between resistance to multiple hormones and AHO features. The most clinically evident abnormality in PHP type 1a is PTH resistance, which presents as hypocalcemia, hyperphosphatemia and an elevated serum PTH level preceding hypocalcemia [5]. Our patient presented with normocalcemia as an adult; however, he had been taking calcium and vitamin D since he was 9 years old. Some patients with PHP type 1a remain normocalcemic throughout their life despite PTH resistance [2].

Resistance to TSH is frequently accompanied by PTH resistance, and both of which clinically manifest during childhood or adolescence [2]. Goiter and antithyroid antibodies are usually absent, as was the case in our patient. Mild TSH resistance due to heterozygous TSH receptor variants suggests that thyroxine may be dispensable [6] because the circulating TSH elevation would compensate for the mild refractoriness in thyroid cells.

Resistance to PTH can be confirmed via the Ellsworth-Howard test because affected individuals have reduced urinary cAMP and phosphate excretion in response to the exogenous administration of biologically active PTH [7]. However, clinical guidelines now indicate that performing the Ellsworth-Howard test is not necessary but might be helpful in research settings [1]. Instead, a molecular test crucially confirms the clinical diagnosis and allows the categorization of the condition of a patient as a subtype of PHP, which can guide management [1]. Although the same missense mutation of the *GNAS* gene (c.478C > T) in our patient had been reported in a patient with AHO [6], it was the first time reported in Korean patients with PHP. Because PHP type 1a is caused by maternally inherited inactivating *GNAS* mutation [8], we assumed that the mother or maternal family may transmit the genetic defect. However, our patient's family could not undergo genetic testing because he had been raised in an orphanage and no record of familial relations was found at the time of this study.

The long-term therapy for hypocalcemia in patients with PHP needs active vitamin D metabolites (calcitriol) or analogues (alfacalcidol) and oral calcium supplements [9]. The current treatment approach is to reduce the serum PTH level to the upper normal limit to avoid suppressing PTH, which can lead to hypercalciuria and renal calcification [1]. Associated endocrinopathies, particularly hypothyroidism, growth hormone deficiency and hypogonadism, when present, should be treated with levothyroxine, sex hormones or growth hormone. Prospective clinical trials focusing on the management and outcomes of treatment for PHP have not been conducted because of the rarity of the disease [1, 10].

In conclusion, we report a case of PHP type 1a confirmed by clinical, biochemical and molecular analyses. Patients with PHP have various endocrinopathies from early childhood to adulthood, which yield a highly heterogeneous clinical picture. Early interventions and multidisciplinary follow-up are necessary for efficient therapeutic management of PHP type 1a.

Ellsworth-Howard test

Time	Urine vol. (ml)	Urine P Consentration (mg/dL)	Urine P Amount (mg)	Urine C-AMP (umol/d)	Cr (mg/dL)	Procedure
7:00						Phosphate restiction diet
9:00						Drinking free water 200 cc
10:00	100	3.5	3.5		46.14	Start after complete urination (drinking free water 200 cc in every hour)
11:00 (U1)	100	1.2	1.2		35.05	
12:00 (U2)	200	6.0	12	0.1	50.18	
13:00 (U3)	100	7.0			41.73	**Teriparatide 40 mcg SQ**
14:00 (U4)	490	8.5	7	0.2	17.68	
15:00 (U5)		22.5	41.65		27.53	

Figure 3. Results of the Ellsworth-Howard test: U1, urine 2 h before teriparatide injection; U2, urine 1 h before teriparatide injection; U3, urine at teriparatide injection; U4, urine 1 h after teriparatide injection; U5, urine 2 h after teriparatide injection. (**a**) Phosphaturic response: (U4 + U5)—(U1 + U2) > 35 mg/2 h, (**b**) cAMP response: U4/U2 > 10.

SUPPLEMENTARY MATERIAL

Supplementary material is available at the *Journal of Surgical Case Reports* online.

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None.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

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ETHICS APPROVAL

This study was reviewed and approved by our Institutional Review Board (IRB No. 2021–08-023).

CONSENT

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

GUARANTOR

Ho Yeon Chung.

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