Case Report

Adult onset pseudohypoparathyroidism type-1b with normal phosphaturic response to exogenous parathyroid hormone

Sandeep Kharb, Abhay Gundgurthi, M. K. Dutta, M. K. Garg
Department of Endocrinology, Army Hospital (Research and Referral), Delhi Cantt, India

ABSTRACT

Pseudohypoparathyroidism type-1b is a hereditary disorder of clinical hypoparathyroidism without AHO phenotype, characterized by blunted nephrogenous cyclic-AMP (cAMP) response to exogenous parathyroid hormone (PTH). Here we report a young adult presenting with hypocalcemic tetany with raised PTH levels. His urinary cAMP response to exogenous PTH (recombinant 1-34) was blunted; however, phosphaturic response was normal.

Key words: Parathyroid hormone, pseudohypoparathyroidism, urinary cyclic-AMP

INTRODUCTION

Pseudohypoparathyroidism (PHP) was first reported in 1942 by Albright who presented 3 cases of hypocalcemia with no response to parathyroid extract and Albright hereditary osteodystrophy (AHO) phenotype of short stature with round facies, obesity, brachydactyly, mental retardation, and subcutaneous calcification.[1] Subsequently it was proved that PHP is caused by resistance to action of parathyroid hormone (PTH) in selective organs with monoallelic expression of Gsα (proximal renal tubules, thyroid, gonads, pituitary), later resistance to PTH was reported in patients with PHP cases without AHO phenotype and normal Gsα activity and it was classified as PHP type-1b (PHP1b) caused due to imprinting defects in GNAS1 gene located on Chromosome 20q13.3.[2] Classically, PHP1b is characterized by blunted nephrogenous cyclic-AMP (cAMP) and phosphaturic response to exogenous PTH. Here we report a case of PHP1b confirmed by blunted urinary cAMP response to exogenous PTH but had normal phosphaturic response on treatment with calcium and vitamin D. We discuss possible mechanisms to explain normal phosphaturic response.

CASE REPORT

A 34-year-old male presented with recurrent carpopedal spasms of 4 years duration with perioral numbness, cramps, muscle twitching and generalized weakness for which he was evaluated 2 years back and found to have hypocalcemia, hyperphosphatemia, hypercalcuiuria, high PTH without AHO phenotype. He was given provisional diagnosis of PHP and started on calcium and 1α-calcidiol. Presently he reported for review. He was symptomatically improved with treatment. There was no family history of similar illness, or bony abnormality. On examination he was 184 cm tall with weight of 78 kg (BMI 23 kg/m²). He had no evidence of AHO phenotype. Latent signs of tetany in the form of positive Chvostek’s sign and Trousseau’s sign were present. We decided to re-evaluate him in view of late age of onset of symptoms, absence of AHO phenotype, and to confirm the diagnosis. His medications were stopped for 7 days. Investigations revealed normal...
renal parameters (serum creatinine, 88.4 µmol/L) and normal serum magnesium (0.86 mmol/L), 25(OH)D levels (137.2 nmol/L) and raised PTH (63 pmol/L). His computed tomography scan of the brain was normal. His bone mineral density (T score, 0.5 at L1–L4 and −0.2 at femur neck) and thyroid function were normal (T3 0.87 ng/mL, T4 7.59 µg/dL, TSH, 2.20 mIU/L). In view of hypocalcemia with raised PTH three possibilities were entertained—idiopathic hypoparathyroidism with heterophile antibody against PTH, PHP1b, or PHP2. For the first possibility his serum was precipitated with polyethylene glycol (PEG) for detection of heterophile antibodies. His PEG precipitated serum PTH levels were also high (61.5 pmol/L). Modified Ellsworth Howard test was planned to differentiate between PHP1b and PHP2. Since this test was performed first time in this institute, it was planned in three subjects: one present case, one healthy age- and sex-matched control and another known case of postoperative hypoparathyroidism. The protocol starts with oral hydration with 200 mL water every 30 min starting at 0600 hours in the morning. Starting from 0830 hours, timed urine collection is done every 30 min and blood samples are collected at midpoint of each till 1100 hours. From 1000 to 1010 hours, teriparatide is infused intravenously in the dose of 5 units/kg (200 units maximum; conversion factor 20 µg = 67 units). Each sample is analyzed for phosphate, creatinine, and additional cAMP in urine samples. Basic parameters of all subjects are depicted in Table 1. The patient had blunted urinary cAMP response to exogenous PTH (recombinant 1-34) as compared to healthy control and patients with postoperative hypoparathyroidism [Figure 1]. However, our patient had normal tubular reabsorption of phosphate and percentage fall in the ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate (TmPO4/GFR) [Figure 2] when compared to two other subjects, indicating normal phosphaturic response. In view of hypocalcemic tetany with raised PTH levels and blunted nephrogenous response to exogenous PTH, the patient was diagnosed as a case of PHP1b. He was continued with calcium and 1α-calcidiol.

**Discussion**

PHP is a genetic disorder characterized by hypocalcemia, hyperphosphatemia, increased concentration of PTH with insensitivity to action of PTH at different sites depending on maternal or paternal imprinting and reduced Gsα activity. GNAS-1 gene is located on Ch 20q13.3 and encodes Gsα. Gsα has biallelic expression in most tissues but paternal gene is silenced in renal proximal convoluted tubule, thyroid, gonads, and pituitary. PHP1a has mutated maternal Gsα. PHP1b is characterized by epigenetic defects in imprinting of GNAS locus of maternal allele due to microdeletions at GNAS-1 locus with normal Gsα activity everywhere but renal proximal tubule. Gsα deficiency in renal proximal tubules is due to the lack of an active maternal allele, but has no effect on Gsα expression in the majority of other tissues, thus lack AHO phenotype.

![Table 1: Basic mineral parameters of case, control, and known hypoparathyroid patients](image)

**Table 1: Basic mineral parameters of case, control, and known hypoparathyroid patients**

| Parameters                  | Case | Control | Postop hypoparathyroidism |
|-----------------------------|------|---------|---------------------------|
| Serum calcium (mg/dL)       | 6.9  | 8.6     | 7.1                       |
| Serum phosphate (mg/dL)     | 7.3  | 3.4     | 6.4                       |
| Urine calcium (mg/24 h)     | 56   | 185     | 92                        |
| Urine phosphate (mg/dL)     | 11.2 | 4.5     | 9.8                       |
| TRP (%)                     | 95.1 | 94.3    | 89.36                     |
| TmPO4/GFR (mmol/L)          | 5.2  | 2.3     | 5.4                       |
| Urine cAMP (mmol/L)         | 0.888| 0.533   | 0.573                     |

TRP: Tubular reabsorption of phosphate, TmPO4/GFR: Ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate

![Figure 1: Urinary cyclic-AMP response to exogenous parathyroid hormone](image)

![Figure 2: Fall in tubular reabsorption of phosphate and TmPO4/GFR in response to exogenous parathyroid hormone](image)
may present as pseudohypoparathyroidism and may have mild resistance to TSH and calcitonin.[2] Biochemically, PHP1b is classically characterized by blunted urinary cAMP and phosphaturic response to PTH.

In our patient, hypocalcemic tetany, raised PTH, and blunted urinary cAMP response to exogenous PTH confirmed the diagnosis of PHP1b. PHP usually presents at an early age but late onset PHP1 at age of 54 years[6] and PHP1b has been reported at 46 years of age.[7] This is the second case in the literature where presentation of the disease delayed beyond third decade. Also about 50% cases of PHP1b are sporadic so family history of similar illness may not be there.

Another odd point in our case was normal phosphaturic response to exogenous PTH. We propose following possible explanations for normal phosphaturic response in our case who, was on treatment. First, it is reported that during in vitro tests, adding serum of pseudohypoparathyroid patient to exogenous PTH leads to blunted phosphaturic response due to the presence of some unknown inhibitory factor in serum of these patients, which reverts on treatment of these patients with vitamin D.[8] It is speculated that this unknown factor is amino-truncated fragments of PTH, which gets accumulated as part of raised PTH. Vitamin D treatment leads to normalization of serum calcium level, which by feedback inhibition of parathyroid glands reduces truncated fragments of PTH. Hence, interference to exogenous PTH is reduced leading to normal phosphaturic response [Figure 3]. Second, PTH resistance and hyperphosphatemia decrease activity of enzyme 1-α-hydroxylase, which lead to decreased generation of 1,25(OH)2D. Activated vitamin D acts on osteoblast and increases the release of FGF-23, which by inducing phosphaturic response to PTH [Figure 4]. Finally, it has been reported in rat hepatocytes that extracellular hypocalcemia leads to intracellular hypocalcemia, which may lead to decreased activity of calcium-dependent enzymes and restoration of extracellular normocalcemia leads to intracellular normocalcemia and subsequent normal activity of intracellular calcium-dependent enzymes.[9] We postulate that these intracellular calcium-dependent enzymes may be playing important role in phosphaturic response to PTH, and thus treatment of patient with vitamin D will lead to restoration of normal phosphaturic response to PTH [Figure 4]. Furthermore, correction of phosphaturic effect with vitamin D treatment is supported by the reports of reversal of all abnormalities mimicking PHP2 in cases of vitamin D deficiency.[11,12]

This suggests that deficiency of 1,25(OH)D might be the cause of hyperphosphatemia in patients with PHP. In our case, although serum 25(OH)D was in the range above vitamin D insufficiency, we hypothesize that insufficient conversion to activated vitamin D (was not measured) led to its deficiency and supplementation with 1-α vitamin D corrected phosphaturic response to exogenous PTH.

**REFERENCES**

1. Albright F, Burnett CH, Smith PH, Parson W. Pseudohypoparathyroidism- An example of ‘Seabright-Bantam syndrome’. Endocrinology 1942;30:922-32.
2. Jan de Beur SM, O’Connell JR, Peila R, Cho J, Deng Z, Kam S, et al. Pseudohypoparathyroidism type Ib locus is linked to a region including GNAS1 at 20 q13.3. J Bone Miner Res 2003;18:424-33.
3. Creighton WD, Lambert PH, Miescher PA. Detection of antibodies and soluble antigen-antibody complexes by precipitation with polyethylene glycol. J Immunol 1973;111:1219-27.
4. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. Ann Intern Med 1988;109:800-4.
5. Weinstein LS, Liu J, Sakamoto A, Xie T, Chen M. GNAS: Normal and abnormal functions. Endocrinology 2004;145:5459-64.
6. Hamilton DV. Familial pseudohypoparathyroidism presenting in adult life. J R Soc Med 1980;73:724-6.
7. Iida S. Case of pseudohypoparathyroidism type 1b diagnosed as having hypocalcemia (in Japanese). Clin Calcium 2005;15:689-93.
8. Rubin M, Rosen CJ. Hypoparathyroidism and Pseudohypoparathyroidism. In: Rosen CJ, editor. Primer on the metabolic bone disease and disorders of mineral metabolism. 7th ed. Washington: ASBMR; 2008. p. 354-61.
9. Chriskatos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: Metabolism. Endocrinol Metab Clin N Am 2010;39:243-53.
10. Barre MG, Haddad P, Provencher SJ, Bilodeau S, Pecker F, Lotersztajn S, et al. Chronic hypocalcemia of vitamin D Deficiency leads to lower intracellular calcium concentrations in rat hepatocytes. J Clin Invest 1994;93:2159-67.
11. Shrirama M, Bhansali A, Velayutham P. Vitamin D Deficiency masquerading as pseudohypoparathyroidism type 2. J Assoc Physicians India 2003;51:619-20.
12. Akın L, Kurtoğlu S, Yıldız A, Akın MA, Kendirici M. Vitamin D deficiency rickets mimicking pseudohypoparathyroidism. J Clin Res Pediatr Endocrinol 2010;2:173-5.

Cite this article as: Kharb S, Gundgurthi A, Dutta MK, Garg MK. Adult onset pseudohypoparathyroidism type-1b with normal phosphaturic response to exogenous parathyroid hormone. Indian J Endocrin Metab 2011;15:337-40.
Source of Support: Nil, Conflict of Interest: None declared.