

## Case Report Article

# A case of Adult onset Pseudohypoparathyroidism yet to be resolved: “No money no genetics”

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### Abstract

Pseudohypoparathyroidism (PHP) is a heterogeneous inherited disease characterized by unresponsiveness to parathyroid hormone (PTH) in its target organs. The constant finding in patients with PHP is hypocalcemia and hyperphosphatemia with elevated serum PTH levels. Several distinct entities cluster this disorder. PHP type 1 differs from PHP type 2 in that there is a reduced urinary cAMP excretion in response to administration of PTH. Here we report a young female with PHP at late-onset, yet to be differentiated between type 1b and type 2 due to economic struggles that most of our patients face now days. Despite the circumstances the patient was put on treatment since diagnosis with improvement of all biochemical parameters and amelioration of symptomatology. Further diagnostic testing will be held as soon as possible to meet the definitive diagnosis.

**Keywords:** Parathyroid hormone, Pseudohypoparathyroidism, Hypocalcemia, Hyperphosphatemia, GNAS

## Introduction

PHP is a rare endocrine disorder presenting with hypocalcemia, hyperphosphatemia and increased PTH values due to a variable resistance to its action in target organs, mainly the proximal renal nephron<sup>1,2</sup>. At present, no data exist about its exact prevalence, although according to Orphanet Report Series it has been estimated to be 0.79/100.000<sup>3</sup>.

Based on the associated somatic and biochemical features PHP is subdivided in different types: PHP type 1a (PHP1a), PHP type 1b (PHP1b), PHP type 1c (PHP1c) and PHP type 2 (PHP2). PHP 1a patients present with a distinctive phenotype called Albright's hereditary osteodystrophy (AHO), characterized by short stature, obesity, round face, brachydactyly and subcutaneous ossifications. The molecular pathogenesis is due to maternally inherited inactivating mutations in the GNAS gene on chromosome 20q that encodes the  $\alpha$ -subunit of the stimulatory G-protein (Gsa). The expression of Gsa in variable tissues explains the variable resistance to multiple hormones that act through it (TSH, ACTH, GHRH, glucagon, gonadotropins)<sup>4,5</sup>. On the other hand, patients with paternally inherited mutations are affected by pseudo-pseudohypoparathyroidism (PPHP), manifesting AHO features without any biochemical alteration. Since Gsa is mainly transcribed from the maternal allele in the tissues such as proximal renal tubule, thyroid

and ovary where PTH, TSH, LH and FSH act respectively, their action is exerted normally if the mutation is transmitted by the paternal allele<sup>6</sup>.

The hallmark of PHP1b is renal unresponsiveness to PTH and absence of either AHO phenotype or resistance to other hormones (in some a mild resistance to TSH is reported)<sup>7</sup>. It is caused by modifications in the methylation pattern of the GNAS locus, namely a loss of methylation in the maternal exon A/B, sometimes in combination with other epigenetic defects in other regions of the locus<sup>8</sup>. PHP1b is transmitted in an autosomal dominant manner (AD-PHP1b), although most of the cases are sporadic<sup>3</sup>. Cases due to paternal 20q dysomies are also reported<sup>9</sup>. Moreover, the hypothesis of an autosomal recessive pattern has also been generated to explain the molecular mechanism of sporadic PHP1b in some kindreds<sup>10</sup>. Clinical diagnosis of PHP1b may be accordant

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Parameters	Results	Reference range
Total Calcium (mg/dl)	<b>6,91</b>	8,2-10,2
Phosphorous (mg/dl)	<b>4,7</b>	2,5-4,5
Magnesium (mEq/l)	1,7	1,5-2,5
Sodium (mEq/l)	144	135 - 145
Potassium (mEq/l)	4,3	3,5-5
Albumin (g/dl)	4,05	3,4-5,4
Creatinine (mg/dl)	0,7	0,5-1,1
BUN (mg/dl)	31	10-50
SGPT (U/l)	12	7-30
SGOT (U/l)	23	9-32
γGT (U/l)	8	5-21
ALP (U/l)	<b>173</b>	35-104
PTH (pg/ml)	<b>133</b>	10-65
25OHvitD3 (ng/dl)	25	>30
TSH (U/ml)	4,1	0,3-5
FT4 (ng/dl)	1,4	0,7-2
Ab anti-TPO (U/ml)	<b>217</b>	<60
Ab anti-TG (U/ml)	<b>764</b>	<60
Urine Calcium (mg/24h)	<b>65</b>	100-300

**Table 1.** Baseline biochemical and hormonal parameters.

with molecular pathogenesis only when PTH resistance is accompanied by the absence of both multiple hormone resistance and AHO features<sup>11</sup>.

PHP2 patients lack the AHO phenotype, maintain a response to cAMP but there is no phosphaturic response after exogenous PTH infusion, due to a molecular defect distal to cAMP generation in the PTH-mediated signal transduction pathway. No genetic abnormalities causing PHP2 are yet identified<sup>12-15</sup>.

## Case report

A 30-year-old female was referred to our clinic because the last three months she was complaining about intermittent perioral numbness, cramps and paresthesia to hands and lower legs. She was passing a difficult time because of family problems and the above symptoms were more pronounced during stress. Analysis showed hypocalcemia, hyperphosphatemia, high PTH and alkaline phosphatase (ALP), normal renal/liver function, albumin, serum magnesium and 25(OH) vitamin D3 (25OHD3) and low urinary calcium during 24hour urine collection. There was a positivity of thyroid antibodies with normal thyroid function (Table 1). Bone mineral density by dual-energy X-ray absorptiometry (DXA) at lumbar spine (z score -0,9) and left

Parameters	6 months	18 months	Reference range
Corrected Calcium (mg/dl)	<b>7,2</b>	8,26	8,2-10,2
Phosphorous (mg/dl)	4,3	4	2,5-4,5
PTH (pg/ml)	<b>72</b>	52,7	10-65
25(OH)vitD3 (ng/dl)	28	30	>30
ALP (U/l)	<b>134</b>	91	35-104
Urine Calcium (mg/24h)	<b>98</b>	150	100-300

**Table 2.** Biochemical and hormonal parameters at 6 and 18 months from baseline.

femur neck (z score -0,5) were both within the normal range. At neck ultrasound operated by an experienced radiologist the sonographic pattern of Hashimoto's thyroiditis was confirmed as well as the presence of mild hyperplasia of both inferior parathyroid glands. On examination she was 160 cm tall with weight of 55 kg (BMI 21.7 kg/m<sup>2</sup>). She had no evidence of AHO phenotype as well as there was no family history of similar illness, or bony abnormality. Menses were regular, she was recently divorced without children and she was not taking any kind of drugs. She was working as a clerk since her twenties until a year ago when she was fired due to economic crisis in our country.

She was given a provisional diagnosis of PHP and started on calcium supplements (calcium carbonate 500 mg twice daily) and 1α-calcidiol (0.5 mcg once daily). She was symptomatically improved with treatment and there was also an amelioration of blood tests at six months' follow-up visit. Nevertheless, calcium supplementation was increased (calcium carbonate 500 mg trice a day) because of persistently low plasma calcium levels and PTH still above normal range. The patient returned for reexamination after one year since her last visit with improvement of all biochemical parameters (Table 2). The neck ultrasound operated by the same radiologist showed normal parathyroid glands. No symptoms of hypocalcemia were referred nor latent sings of tetany in the form of positive Chvostek's and Trousseau's were present on examination. Given the childbearing age of the patient it was recommended to proceed to further investigation (Ellsworth-Howard Test and/or genetic testing) but she denied because had no health insurance by the time and therefore she could not economically afford it.

## Discussion

Hypocalcemia is a relatively usual finding in every day clinical practice. However, unmasking the underlying cause of hypocalcemia can be complicated and often perplexing. Hypocalcemia with a normal to elevated serum phosphate

level are usually due to chronic renal disease, whereas the abiding cases are caused either by impaired PTH secretion such as in hypoparathyroidism or by resistance to its actions<sup>16-18</sup>. PHP is a genetic disorder related to increased secretion of PTH and target-tissue unresponsiveness to its biological actions, mainly in the proximal nephron. In PHP patients, biochemical findings (hypocalcemia and hyperphosphatemia) resemble that of hypoparathyroidism. PHP type 1a is characterized by hormone resistance accompanied with a cluster of developmental and somatic defects that are overall defined as AHO. Both PHP type 1b and PHP type 2 patients present with PTH resistance in the absence of AHO's phenotype but they differ since PHP type 1b patients fail to show adequate increases in the urinary excretion of either cAMP or phosphate while those with PHP type 2 exhibit normal urinary excretion of cAMP but an impaired phosphaturic response during Ellsworth-Howard test<sup>17-19</sup>. PHP type 2 is a very rare disorder that was first reported by Drezner et al. in 1973 and until to date very few cases have been documented<sup>20,21</sup>. Unlike PHP type 1, the clinical mechanisms of abnormal PTH signaling in PHP type 2 remain obscure. Furthermore, it is questionable if PHP type 2 should stand as a disease entity because the results of the Ellsworth-Howard test in some patients with vitamin D deficiency and/or renal tubular damage resemble those of PHP type 2<sup>19,22-25</sup>. In our patient, the clinical findings and initial laboratory results suggested PHP type 2 or PHP type 1b. In both forms Albright's phenotype is absent and patients may never develop severe PTH resistance, whereas some seem to "outgrow" their resistance<sup>14,26,27</sup>. Indeed in our patient diagnosis was made at her thirties during a period of stress which is well known to favor symptomatic hypocalcemia due to respiratory alkalosis and a consequent higher binding of calcium to albumin. Vitamin D deficiency mimicking PHP type 2 can be excluded since levels of 25OHvitD3 were sufficient at initial testing and through the entire laboratory follow-up.

At baseline our patient showed an increased alkaline phosphatase activity that progressively ameliorated by treatment, with bone densitometry at lumbar spine and femoral neck within the normal range according to her age. In literature exists heterogeneity in the skeletal phenotype among patients with PHP, primarily those with PHP type 1b. In some cases is reported a clinical picture of accelerated subperiosteal resorption, osteitis fibrosa cystica and elevated bone turnover markers, such as that of hyperparathyroid bone disease<sup>28</sup>. On the other hand they have been described cases with no pathological findings at densitometry or mild osteopenia whereas occurrence of osteosclerosis at radiographs and bone histomorphometry has been also reported<sup>4,29,30</sup>.

Our patient presented at diagnosis with mild hyperplasia of the lower parathyroid glands, probably due to long standing untreated PHP, that regressed after adequate treatment with calcium and vitamin D supplementation in the absence of hypercalciuria as often is seen in primary

hypoparathyroidism during the effort to normalize serum calcium. PHP patients are still responsive to the calcium-reabsorbing action of PTH in the distal tubule and therefore unlike primary hypoparathyroidism patients, do not usually develop hypercalciuria or nephrocalcinosis even on treatment<sup>31-33</sup>. However, most PHP patients are treated to raise calcium into a range that alleviates symptoms but not high enough to normalize PTH. Some authors recommend that the goal of treatment should be to normalize serum calcium and PTH levels or to get the PTH as low as possible without causing hypercalcemia or hypercalciuria with the aim to prevent the complications of hyperparathyroid bone disease and tertiary hyperparathyroidism<sup>31</sup>. In our case at six months from initial evaluation calcium supplementation was increased, based primarily on biochemical parameters, which may have later contributed to the change of sonographic pattern of parathyroid glands.

Most cases of PHP type 2 are preceded by or simultaneously present with autoimmune disorders, such as Sjögren's syndrome and thyroid autoimmune disease. It is believed that autoimmunity may have a causative effect on hypocalcemia associated with a discrepancy between urinary cAMP excretion and the phosphaturic actions of PTH. Indeed, Yamada et al. studied the effects of serum immunoglobulin G obtained from a patient with PHP type 2 and Sjögren's syndrome on the renal function in rats<sup>16,34</sup>. That study demonstrated that interaction between autoantibodies and the components of the renal tubular plasma membrane can inhibit the occurrence of PTH-induced phosphaturia<sup>16,35</sup>. Since our patient had Hashimoto's thyroiditis diagnosis of PHP type 2 is probable.

The limit of our study is that diagnosis of PHP is based solely on biochemical criteria and normalization of blood analysis after commencing the treatment indicated in these cases. Unfortunately in our patient a distinction between PHP type 1b and PHP type 2 and eventually further genetic testing cannot be made until the renewal of her public health insurance. By that time we hope more light will be shed on the diagnostic criteria and classification of these rare and highly heterogeneous diseases as recently proposed by the European PHP network<sup>36</sup>.

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