

Brief Report

Calcitriol and Levothyroxine Dosing for Patients With Pseudohypoparathyroidism

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Abbreviations: BMI, body mass index; Gs α , stimulatory G protein; PAG, PTH levels at goal; PHP, pseudohypoparathyroidism; PHP1A, pseudohypoparathyroidism type 1a; PNAG, PTH levels not at goal; PTH, parathyroid hormone; T4, thyroxine; TAG, TSH and free T4 at goal; TNAG, TSH and/or free T4 levels not at goal; TSH, thyrotropin (thyroid stimulating hormone).

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Abstract

Pseudohypoparathyroidism (PHP) is a rare hormone resistance syndrome caused by mutations in *GNAS*. This cross-sectional study investigated whether PHP patients with parathyroid hormone (PTH), thyrotropin (thyroid stimulating hormone; TSH), and free thyroxine (T4) levels at goal required higher doses of levothyroxine and calcitriol than recommended by current guidelines to overcome mineral ion abnormalities due to hormone resistance.

Baseline demographic and clinical data of participants enrolled in PHP research studies between 2012–2021 were collected via retrospective chart review. Longitudinally, data were recorded at a maximum frequency of once a year starting at 1 year of age. The PTH at goal (PAG) group was defined as PTH < 150 pg/mL and calcium \geq 8.4 mg/dL, and the TSH and free T4 at goal (TAG) group was defined as TSH < 5 mIU/L and free T4 \geq 0.8 ng/dL.

The PAG group (n = 74) was prescribed higher calcitriol doses than the PTH not at goal (PNAG) group (n = 50) (0.9 ± 1.1 vs 0.5 ± 0.9 mcg/day, $P = 0.04$) and 21% of individual patients were prescribed ≥ 1.5 mcg of calcitriol daily. This remained true after normalization for body weight (0.013 ± 0.015 vs 0.0067 ± 0.0095 mcg/kg/day, $P = 0.008$). There was no statistically significant difference in levothyroxine dosing between the TAG group (n = 122) and TSH and free T4 not at goal (TNAG) group (n = 45) when normalized for weight (2.0 ± 0.7 vs 1.8 ± 0.7 mcg/kg/day, $P = 0.2$).

More than one-third of patients with PHP had PTH levels not at goal and some patients required calcitriol doses ≥ 1.5 mcg/day to meet current treatment goals.

Key Words: pseudohypoparathyroidism, Albright hereditary osteodystrophy, levothyroxine, calcitriol, PTH resistance, TSH resistance

Pseudohypoparathyroidism (PHP) is a rare hormone resistance syndrome caused by mutations in the *GNAS* gene which encodes the α subunit of the stimulatory G-protein (G_{α}) [1, 2]. Pseudohypoparathyroidism type 1a (PHP1A) is caused by loss of function mutations on the maternal *GNAS* allele. Lack of normal G_{α} expression results in abnormal G-protein coupled receptor (GPCR) function. The resulting phenotype occurs due to disruptions in the G_{α} -mediated cyclic AMP second messenger signaling pathway which is utilized for many hormones, including parathyroid hormone (PTH) and thyrotropin (thyroid stimulating hormone; TSH) but also luteinizing hormone, follicle-stimulating hormone, and growth hormone-releasing hormone. Due to tissue specific imprinting of *GNAS* in regions such as the pituitary, thyroid, gonads, renal proximal tubules, and hypothalamus, patients with PHP1A have significantly reduced G-protein coupled receptor function, leading to multi-hormone resistance [3-5]. Abnormal methylation of *GNAS*, referred to as type 1b (PHP1B), also causes abnormal G_{α} expression and clinically significant hormone resistance [6].

The most common forms of hormone resistance in PHP are resistance to PTH and TSH [7]. TSH resistance is often present at birth and can be identified on newborn screening tests, often requiring relatively low and stable levothyroxine supplementation [1]. In contrast, there is postnatal reduction of the paternal G_{α} expression in the proximal renal tubules [1, 8]. PTH resistance typically presents post-infancy with an asymptomatic increase in PTH that if untreated progresses to hypocalcemia. Historically, PTH resistance was treated according to hypoparathyroidism guidelines with calcitriol doses titrated to achieve low-normal calcium levels for fear of overtreatment leading to urine hypercalcemia and subsequently nephrocalcinosis. However, a 2012 report of 5 cases of tertiary hyperparathyroidism in adults with PHP1B raised concern that prolonged exposure to high PTH levels can itself have deleterious effects such as tertiary hyperparathyroidism and hyperparathyroid bone disease [9]. In addition, patients with PHP are at lower risk of renal complication due to preserved anticalciuric effects of PTH on the distal renal tubules [10]. Recent international treatment guidelines now recommend maintaining calcium levels that are on the upper end of normal or slightly elevated to sustain PTH-dependent calcium reabsorption in the distal convoluted tubules [11, 12].

To overcome mineral ion abnormalities due to intrinsic hormone resistance, high medication doses may be required. There are no published dosing guidelines for levothyroxine or calcitriol in patients with PHP, and physicians may be hesitant to prescribe medication doses outside the typical range for hypoparathyroidism and hypothyroidism. To better understand the natural history of hormone resistance

in PHP and the range of medication dose requirements, we undertook a retrospective chart review of patients in our PHP research database.

Methods

Participants

The study protocol was approved by the Vanderbilt Institutional Review Board. Participants in this cross-sectional study included all participants enrolled in PHP research studies at Vanderbilt University Medical Center between 2012 and 2021 (NCT02411461, NCT03029429, NCT04551170, NCT03761290, and the PHP Natural History Study). If genetic testing results were unavailable, patients were included if they met the clinical diagnostic features: PTH resistance and/or ectopic ossifications and/or early-onset obesity (before 2 years of age) associated with TSH resistance and/or Albright hereditary osteodystrophy [11, 12]. Patients with pseudo-PHP were not included as they lack hormone resistance.

Data Collection

Data were collected via retrospective chart review and included any available data from commercial laboratories and outside clinics/hospitals. We extracted demographic information, anthropomorphic data, laboratory data, genetic testing results and medications for each subject. Body mass index (BMI) z-scores and percent of the 95th percentile were obtained from the Centers for Disease Control growth charts. In cases of severe obesity, percent of the 95th percentile is the preferred expression of BMI in children [13]. Data were collected starting at 1 year of age or at the age where the first pieces of laboratory data and medication information were available. Data was subsequently recorded every 12 months (\pm 3 months).

According to international guidelines, PTH resistance is defined as any elevation in serum levels of PTH which usually begins in early childhood and results in subsequent changes in serum levels of calcium and phosphorous [12]. Calcium should be normal and PTH levels for patients with PHP should be within the mid-normal to up to 2 times the upper limit of the normal range to minimize adverse effects on skeletal mineralization and the growth plates [11, 12]. Serum PTH levels of ≥ 150 pg/mL approximates greater than 2 times the upper limit of the normal range on most assays. We used PTH ≥ 150 pg/mL or the presence of hypocalcemia (calcium < 8.4 mg/dL) to create a priori cutoff values and differentiate between patients who have PTH levels not at goal (PNAG) vs PTH levels at goal (PAG, PTH < 150 pg/mL, calcium ≥ 8.4 mg/dL). Similarly, TSH resistance according to international guidelines is defined by

elevated serum levels of TSH and thyroid hormones that can be normal or slightly reduced [11, 12]. Thus, we defined those who had TSH and free T4 levels at goal (TAG) as TSH < 5 mIU/L and free T4 \geq 0.8 ng/dL and those who had TSH and/or free T4 levels not at goal (TNAG) as TSH > 5 mIU/L and/or free T4 < 0.8 ng/dL.

Data Analysis

Parametric statistical analyses were performed using SPSS, version 27, software. All data are presented as mean \pm SD. $P < 0.05$ was considered statistically significant.

Results

Study Population

The study database included 34 patients with PHP, 24 (71%) females and 10 (29%) males, shown in Table 1. Thirty-two patients had genetic testing; 24 patients had a variant in *GNAS* consistent with PHP1A, and 3 patients had a pathogenic variant in *STX16*, consistent with PHP1B. Five patients had negative testing of *GNAS* without further genetic evaluation and 2 patients had not had any genetic testing. There were 171 patient encounters with 25 patients (74%) having 2 or more years of data available. Twelve of the patients (48%) with longitudinal data received at least some of their clinical care at Vanderbilt University Medical Center.

PTH Resistance

PTH resistance was present in all subjects. There were 5 patients with documented PTH levels before and after onset of PTH resistance; onset occurred at 1, 1, 5, 12, and 13 years old. Calcitriol dose was correlated with age (β 0.4, r^2 0.2, $P < 0.001$, $n = 170$, Fig. 1), but this was driven by the PNAG group. When the PAG group was analyzed separately, the correlation was not significant (β 0.2, r^2 0.04, $P = 0.08$, $n = 73$). In the PAG group, there was no difference between calcitriol dose in pre-pubertal ($n = 39$) vs post-pubertal patients ($n = 35$, girls \geq 14 years old, boys \geq 16 years old) (0.7 ± 0.9 vs 1.1 ± 1.4 mcg/day, $P = 0.07$; 0.13 ± 0.02 vs 0.13 ± 0.01 mcg/kg/day, $P = 1$).

There were 124 encounters for 34 patients with PTH resistance and a PTH and/or calcium level. This group was 73% female and 12.2 ± 7.0 years old (range, 1-55 years). A comparison of patients with PAG vs PNAG is presented in Table 2. The PAG group ($n = 74$) had higher calcitriol doses than the PNAG group ($n = 50$) (0.9 ± 1.1 vs 0.5 ± 0.9 mcg/day, $P = 0.04$, Fig. 2). This remained true after normalization for body weight (0.013 ± 0.015 vs 0.0067 ± 0.0095 mcg/kg/day, $P = 0.008$). At their most recent visit, 21%

of individual patients were prescribed ≥ 1.5 mcg of calcitriol daily.

There was no difference in calcium supplementation between groups (Table 2) and most patients were not taking a calcium supplement (57% of PAG group and 68% of the PNAG group). Only 21% of encounters included a urine calcium/creatinine ratio. Urine calcium/creatinine ratio was inversely correlated with PTH level after adjusting for calcitriol dose (β -0.6, r^2 0.3, $P = 0.003$). Five of those 36 encounters had a urine calcium/creatinine ratio > 0.22 mg/mg which was typically transient and not associated with nephrocalcinosis on ultrasound. All patients with an elevated urine calcium/creatinine ratio had a PTH level between 25 and 50 pg/mL ($n = 4$, 1 patient did not have a simultaneous PTH level available). Phosphorus levels were lower in the PAG group ($n = 30$) than the PNAG group ($n = 22$) (4.6 ± 0.7 vs 5.7 ± 1.2 , $P < 0.001$). Vitamin D levels were similar between the PAG ($n = 40$) and PNAG ($n = 16$) groups (32 ± 11 vs 28 ± 8 ng/mL, $P = 0.2$).

We were unable to analyze the PHP1B patients separately as there were only 8 encounters and 50% were in the PNAG group. In the PAG group, the PHP1B patients were 15 ± 4.2 years and prescribed 1.9 ± 2.8 mcg/day calcitriol.

TSH Resistance

TSH resistance was present in 33 out of 34 subjects. The patient without TSH resistance had negative testing for PHP1A; he was diagnosed with PHP1B as he had a history of profound PTH resistance with hypocalcemia, normal vitamin D levels and low urinary calcium excretion. Eleven subjects had been tested for evidence of autoimmune thyroiditis; all had negative thyroid peroxidase antibodies. In patients with TSH resistance, it was present in the initial encounter, including in 9 patients with data from 1 year of age. A comparison of the TAG ($n = 122$) and TNAG ($n = 45$) groups is presented in Table 3. The TNAG group was more obese (33.6 ± 10.5 vs 28.9 ± 6.5 kg/m², $P = 0.007$). There was no statistically significant difference in levothyroxine dosing between the TAG and TNAG groups when normalized for weight (2.0 ± 0.7 vs 1.8 ± 0.7 mcg/kg/day, $P = 0.2$).

We examined the 122 encounters in which patients had TSH and free T4 levels at goal. Levothyroxine dosage (mcg/kg/day) was correlated with age (β -0.6, r^2 0.3, $P < 0.001$). Table 4 presents levothyroxine doses for the age groups defined by the Food and Drug Administration (FDA) levothyroxine package insert.

Discussion

Current practice guidelines for managing PTH resistance in PHP indicate that providers should use active vitamin

Table 1. Baseline characteristics

Age range of Sex patient data			Genetic testing results	Clinical diagnosis	Sub-cutaneous ossification	PTH resistance	TSH resistance
1	3-22	Female	WES negative	PHP1A	Yes	Yes	Yes
2	8-16	Male	GNAS c. C728T p.A243V, pathogenic	PHP1A	No	Yes	Yes
3	5-18	Female	GNAS c. C728T p.A243V, pathogenic	PHP1A	No	Yes	Yes
4	14-17	Female	GNAS c.C396T p.I132I, c.C1116T p.N372N, c.C558T p.I186I, all polymorphisms	PHP1A	Yes	Yes	Yes
5	28	Female	GNAS c.C7121T, benign	PHP1A	No	Yes	Yes
6	12-16	Male	GNAS Intron 5 c0.846 + 1G>T, pathogenic	PHP1A	Yes	Yes	Yes
7	18-19	Female	GNAS c.C85T, p.Q29X, pathogenic	PHP1A	Yes	Yes	Yes
8	1-12	Female	GNAS c.C34T, p.Q12X, pathogenic	PHP1A	Yes	Yes	Yes
9	8-13	Male	GNAS p.Trp234X, pathogenic	PHP1A	Yes	Yes	Yes
10	1-16	Female	c0.1107delTG, pathogenic	PHP1A	Yes	Yes	Yes
11	11-14	Female	GNAS – no variants found	PHP1A	No	Yes	Yes
12	16-25	Female	WES – GNAS insertion with frameshift in a coding region exon 1 (position 58910723), pathogenic	PHP1A	Yes	Yes	Yes
13	8-14	Female	GNAS intron 4 c0.312 + 5G>A, pathogenic	PHP1A	Yes	Yes	Yes
14	28	Female	WES – GNAS early stop codon in Exon 1 (position 58903550)	PHP1A	Yes	Yes	Yes
15	16-21	Male	GNAS- no variants found	PHP1B	No	Yes	No
16	1-13	Female	GNAS c.C1024T, p.R342X, pathogenic	PHP1A	Yes	Yes	Yes
17	15-18	Female	STX16 deletion	PHP1B	No	Yes	Yes
18	7-12	Female	c.G125A, p.R42H, pathogenic	PHP1A	No	Yes	Yes
19	1-17	Female	GNAS c.C1024T, p.R342X, pathogenic	PHP1A	Yes	Yes	Yes
20	17	Female	GNAS c.GACT568del p.DY190fs, pathogenic	PHP1A	Yes	Yes	Yes
21	9	Male	GNAS exon 13 c0.1100_1101insA, pathogenic	PHP1A	Yes	Yes	Yes
22	1-14	Male	GNAS c.TTC1166del p.LR389del, pathogenic	PHP1A	No	Yes	Yes
23	13	Female	GNAS c.CTGA187del, pathogenic	PHP1A	Yes	Yes	Yes
24	10	Female	GNAS c.GACT585del, pathogenic	PHP1A	Yes	Yes	Yes
25	1-13	Female	No testing done	PHP1A	Yes	Yes	Yes
26	13	Male	STX16 deletion	PHP1B	No	Yes	Yes
27	9-13	Male	STX16 deletion	PHP1B	No	Yes	Yes
28	1-16	Male	GNAS Intron 4 IVS4 + 5G>C, pathogenic	PHP1A	No	Yes	Yes
29	1-9	Female	GNAS c0.344C>T, p.P115L, pathogenic	PHP1A	No	Yes	Yes
30	1	Female	GNAS c0.432 + 2_432 + 15del14IVS + 15del14, pathogenic	PHP1A	Yes	Yes	Yes
31	55	Female	No testing done	PHP1A	Yes	Yes	Yes
32	3-11	Female	c0.348delC GNAS pathogenic	PHP1A	Yes	Yes	Yes
33	27	Male	GNAS c.GACT565del4, pathogenic	PHP1A	Yes	Yes	Yes
34	3-10	Female	GNAS c0.34C>T, pathogenic	PHP1A	No	Yes	Yes

Results presented as mean ± SD. Abbreviations: PHP1A, pseudohypoparathyroidism type 1a; PHP1B, pseudohypoparathyroidism type 1b; WES, whole exome sequencing.

D metabolites or analogs with or without oral calcium supplementation to maintain serum levels of calcium and phosphorus within the normal range while avoiding hypercalciuria. Oral calcium supplementation may be needed, as calcium is an under-consumed micronutrient in the average USA diet [14]. Treatment with active vitamin D analogs should be considered when PTH is more than

2 times the upper limit of normal to minimize adverse effects on skeletal and growth plate mineralization [11, 12]. Nutritional vitamin D deficiency must be excluded before making a diagnosis of PHP. These clinical practice guidelines were created in the context of few studies focused on the natural history and management of PTH resistance in PHP and correspond to current practice guidelines on

primary hypoparathyroidism unrelated to hormone resistance disorders. Standard dosing guidelines for calcitriol in patients with primary hypoparathyroidism recommend an initial dose of 0.25 mcg/day titrated up to 2 mcg daily to maintain serum calcium levels within the normal range [15]. Our results suggest that patients with PHP require

higher doses of calcitriol with a mean dose of 0.9 mcg/day and some patients requiring more than 2 mcg/day. Some patients may benefit from higher doses, as 40% of patient encounters demonstrated PTH levels not at goal. As PHP is a hormone resistance syndrome, higher doses of vitamin D

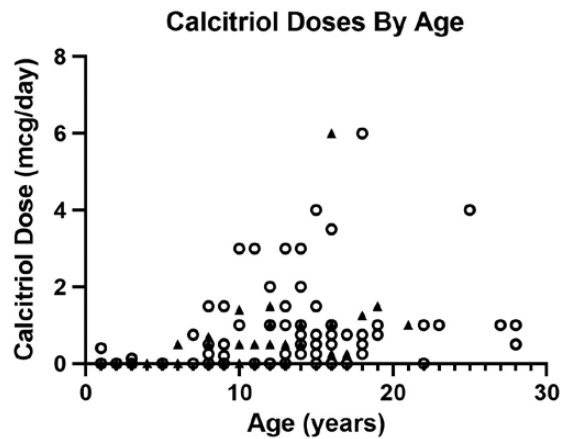


Figure 1. Range of calcitriol doses (mcg/day) of patients at various ages (years). This figure compares patients with PTH levels at goal (PTH < 150, open circles) and PTH levels not at goal (PTH ≥ 150 and/or calcium < 8.4 mg/dL, solid triangles). Data from 1 patient were not included as their age was out of range.

Calcitriol Doses by PTH level

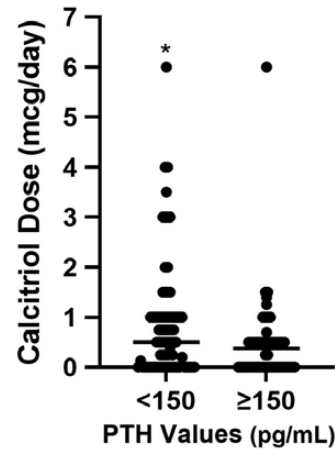


Figure 2. Compares average calcitriol doses (mcg/day) between patients with PTH levels at goal (PAG, 0.9 ± 1.1 mcg/day) and PTH levels not at goal (PNAG, 0.5 ± 0.9 mcg/day). PTH level at goal was defined as PTH < 150 pg/mL; PTH level not at goal was defined as PTH ≥ 150 pg/mL and/or calcium < 8.4 mg/dL. ***P* value of 0.04.

Table 2. Baseline characteristics, laboratory values and medication dosing for patients with PTH levels at goal (PAG) and PTH levels not at goal (PNAG)

	PTH level at goal (PAG) (n = 74)	PTH level not at goal (PNAG) (n = 50)	<i>P</i> value
Age (years)	13.9 ± 7.5	9.7 ± 5.0	<0.001
Gender (% male)	27	28	0.9
Weight (kg)	72.4 ± 28.5	57.7 ± 28.3	0.006
BMI (kg/m ²)	32.9 ± 9.0	30.4 ± 7.4	0.1
BMI z-score	2.23 ± 0.78	2.44 ± 0.80	0.2
BMI (% of the 95 th percentile)	129 ± 30	127 ± 38	0.8
PTH (pg/mL)	73 ± 36	385 ± 267	<0.001
Calcium (mg/dL)	9.6 ± 0.5	8.8 ± 1.1	<0.001
Phosphorus (mg/dL)	4.6 ± 0.7	5.7 ± 1.2	<0.001
25OH-vitamin D (ng/mL)	32 ± 11 (n = 40)	28 ± 8 (n = 16)	0.1
Urine calcium/creatinine ratio (mg/mg)	0.18 ± 0.11 (n = 18)	0.03 ± 0.03 (n = 13)	<0.001
Calcitriol (mcg/day)	0.9 ± 1.1	0.5 ± 0.9	0.04
Calcitriol (mcg/kg/day)	0.013 ± 0.015	0.0067 ± 0.0095	0.008
Calcium supplement (mg/day elemental calcium)	460 ± 738	409 ± 821	0.2
Vitamin D supplement (IU/day)	760 ± 2049	351 ± 1425	0.2

Results presented as mean ± SD. PTH level at goal was defined as PTH < 150 pg/mL. PTH level not at goal was defined as PTH ≥ 150 pg/mL or calcium < 0.84 mg/dL. BMI z-score and percent of the 95th percentile was obtained for patients 2 years and older using the CDC growth charts. Laboratory results were obtained from the medical record and multiple laboratory systems were used. For reference, the Vanderbilt University Medical Center reference ranges are provided: PTH (1-9 years old (yo): 16-63 pg/mL, 9-17 yo: 22-88 pg/mL, 17-19 yo: 16-60 pg/mL, ≥19 yo: 16-77 pg/mL), calcium (2-12 yo: 8.8-10.8 mg/dL, ≥12 yo: 8.4-10.5 mg/dL), phosphorous (1-4 yo: 4.3-6.8 mg/dL, 5-12 yo: 4.1-5.9 mg/dL, 13-15 yo: 3.2-6.2 mg/dL, 16-18 yo: 2.9-5 mg/dL, ≥19 yo: 2.3-4.7 mg/dL), 25OH-vitamin D (≥ 20 ng/mL).

Table 3. Baseline characteristics, Laboratory values and medication dosing for patients with TSH and free T4 levels at goal (TAG) and TSH and free T4 levels not at goal (TNAG)

	TSH and free T4 levels at goal (n = 122)	TSH and free T4 levels not at goal (n = 45)	P value
Age (years)	10.4 ± 6.9	10.3 ± 6.0	1
Gender (% male)	30	29	0.9
BMI (kg/m ²)	28.9 ± 6.5	33.6 ± 10.5	0.007
BMI Z-score	2.39 ± 0.85	2.47 ± 1.1	0.6
BMI (% of the 95 th percentile)	125 ± 27	141 ± 42	0.03
TSH (mIU/L)	2.4 ± 1.4	6.9 ± 3.0	<0.001
Free T4 (ng/dL)	1.1 ± 0.3	1.2 ± 1.9	0.8
Levothyroxine (mcg/day)	98 ± 45	125 ± 94	0.06
Levothyroxine (mcg/kg/day)	2.0 ± 0.7	1.8 ± 0.7	0.2

Results presented as mean ± SD. TSH and free T4 levels at goal was defined as TSH < 5 mIU/L and free T4 ≥ 0.8 ng/dL. TSH and free T4 levels not at goal was defined as TSH ≥ 5 mIU/L and free T4 < 0.8 ng/dL. BMI z-score and percent of the 95th percentile was obtained for patients 2 years and older using the CDC growth charts. Laboratory results were obtained from the medical record and multiple laboratory systems were used. For reference, the Vanderbilt University Medical Center reference ranges are provided: TSH (1-13 years old (yo): 0.73-4.09 mIU/mL, 14-18 yo: 0.47-3.41 mIU/mL, ≥19 yo: 0.35-3.6 mIU/mL), FT4 (≥1 yo: 0.89-1.37 ng/dL).

Table 4. Standardized age-based levothyroxine doses compared with levothyroxine requirements for PHP patients with TSH and free T4 levels at goal (defined as TSH < 5 mIU/L and free T4 ≥ 0.8 ng/dL)

Age group	Levothyroxine package insert (mcg/kg)	Observed levothyroxine dose (mcg/kg)	Observed levothyroxine dose (mcg)	BMI (kg/m ²)	BMI z-score	BMI % of the 95 th percentile
1-5 years (n = 30)	5-6	2.7 ± 0.8	62 ± 14	25.2 ± 4.1	3.46 ± 0.92	140 ± 24
6-12 years (n = 51)	4-5	1.9 ± 0.6	98 ± 45	28.1 ± 5.4	2.31 ± 0.39	128 ± 22
13-15 years (n = 19)	2-3	1.6 ± 0.5	122 ± 46	30.5 ± 5.8	1.92 ± 0.61	110 ± 33
≥16 years (n = 22)	1.6	1.5 ± 0.4	125 ± 40	34.4 ± 8.2	1.81 ± 0.65	116 ± 26

Results presented as mean ± SD. BMI z-score and percent of the 95th percentile was obtained for patients 2 years and older using the CDC growth charts.

analogs may be necessary to address PTH resistance compared with doses that clinicians may consider adequate based on clinical experience and hypoparathyroidism practice guidelines.

Postnatal imprinting of *GNAS* in the renal cortex leads to impaired PTH signaling in the proximal renal tubules [1, 8]. PTH resistance typically presents post-infancy with an asymptomatic increase in PTH that if untreated progresses to hypocalcemia. Young patients with PHP who may be predisposed to PTH resistance can benefit from regular monitoring of serum PTH and calcium levels and more aggressive treatment with calcitriol and vitamin D than patients with hypoparathyroidism, to prevent development of hypocalcemia. In fact, current hypoparathyroidism practice guidelines caution against using high doses of vitamin D analogues to avoid hypercalciuria and subsequent nephrocalcinosis, which would be manifest by a suppressed PTH level [11, 12]. However, patients with PHP have a lower risk of developing hypercalciuria due to preserved sensitivity to PTH in the distal convoluted tubule [11, 12]. We did observe hypercalciuria in 5 patient encounters; all were transient and none had evidence of nephrocalcinosis, consistent with the literature [16]. Of note, all patients

with hypercalciuria had a PTH level between 25-50 pg/mL, suggesting that patients with normal PTH levels may need closer monitoring. Regular monitoring of urine calcium levels along with age-appropriate renal imaging in patients with persistent hypercalciuria are recommended to evaluate for nephrocalcinosis [11, 12].

When compared to FDA package inserts of age-based levothyroxine dosing, younger PHP patients (1-15 years old) required lower weight-normalized doses of levothyroxine than recommended by current guidelines. We hypothesize that this finding may be due to the severity of obesity in the younger patients. The severity of obesity decreased with increasing age as shown by the BMI z-score and BMI as a percent of the 95th percentile. In addition, recent evidence suggests that patient features such as height can influence levothyroxine requirements [17].

One limitation of this study is the small sample size of patients with PHP as this disease is very rare. In addition, this study utilized multiple data points from the same patients at various ages. Due to the minimal selection criteria of the study population and the fact that the participants enrolled in PHP research studies and clinical trials at Vanderbilt University Medical Center from 2012

to 2021 had the opportunity to participate in studies remotely, we expect this study to be generalizable to the USA population of individuals clinically diagnosed with PHP. Participants were recruited throughout the United States and Canada and managed by a wide range of local physicians, thus decreasing the possible confounding variables such as local practice trends, socioeconomic status, and race/ethnicity. Any patient with a clinical diagnosis of PHP was included in these research studies to reflect clinical practice. There was an inadequate number of patients diagnosed with PHP1B to compare differences in hormone resistance and treatment patterns between various subtypes. Thus, there may be underlying differences in PTH and TSH resistance based on underlying genetics that were not accounted for. A larger sample size of participants is necessary to compare PTH and TSH resistance among PHP subtypes.

In conclusion, patients with PHP may require higher doses of vitamin D analogues to adequately manage PTH resistance. With further studies evaluating the natural history and management of the hormone resistances related to PHP, clinicians can gain more confidence and assurance in using higher doses of activated vitamin analogs and calcium for treatment of their patients.

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Disclosures

The authors have nothing to disclose.

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