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Prevalence of Nephrocalcinosis in Pseudohypoparathyroidism: Is Screening Necessary?

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Abstract

The prevalence of nephrocalcinosis in persons with pseudohypoparathyroidism (PHP) has not been systematically examined. We conducted a retrospective study of renal imaging and biochemical results in 19 patients with PHP with 49 imaging assessments. No cases of nephrocalcinosis were identified. Routine screening for nephrocalcinosis in PHP may not be necessary.

Keywords

calcium; parathyroid hormone; PTH; phosphate; pseudohypoparathyroidism

Pseudohypoparathyroidism (PHP) is a rare hormone resistance syndrome caused by mutations in the *GNAS* gene, encoding the α subunit of the stimulatory G protein ($G_s\alpha$)[1, 2]. This protein is a key regulator of the cyclic AMP second messenger signaling pathway for many hormones.[3] Individuals with PHP have resistance to parathyroid hormone (PTH) and may also manifest the Albright hereditary osteodystrophy (AHO) phenotype (stocky build, short stature, round facies, brachydactyly, and variable intellectual disability).[4, 5] Various sub-types of PHP have been described. Some individuals may have resistance to additional hormones, such as thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone and growth hormone releasing hormone. The mechanisms for various features and sequelae including craniosynostosis, premature closure of the epiphysis despite growth hormone deficiency (from resistance to growth hormone releasing hormone), early onset-

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obesity, intellectual disability and the relative contribution of mineral metabolism abnormalities versus other hormone resistances remain uncertain.

PTH binds to receptors in the bone and kidney to regulate calcium homeostasis. PTH stimulates 25-hydroxyvitamin D 1-α hydroxylase gene transcription in the renal proximal tubule to produce active 1,25-dihydroxyvitamin D3 (calcitriol). Activated vitamin D enhances intestinal calcium and phosphate absorption. At the renal proximal tubule, PTH inhibits phosphate reabsorption, while increasing reabsorption of calcium in the distal nephron.[6] Thus, hypoparathyroidism results in hypocalcemia and hyperphosphatemia.

In contrast to hypoparathyroidism, individuals with PHP develop elevated PTH concentrations due to resistance and impaired signaling at the PTH receptor. However, as a result of imprinting and the resulting tissue-specific allelic expression of *GNAS*,[7, 8] the proximal renal tubule has resistance to PTH, which leads to hyperphosphatemia and impaired production of 1,25-dihydroxyvitamin D3, while the distal tubule maintains its anticalciuric response to PTH. Clinical evidence of PTH resistance develops over time with elevated PTH concentrations generally preceding hyperphosphatemia and subsequently hypocalcemia is detected in PHP at a median age of 6 years.[4]

The long-term consequences of chronically high PTH levels in PHP remain to be determined. Furthermore, the optimal treatment targets in regards to serum PTH, calcium and phosphorus concentrations are not known. Both hypoparathyroidism and PHP are treated with calcitriol and calcium supplementation.[9] Treatment is not benign as hypercalciuria is common. Consequently, out of 29 children diagnosed with hypoparathyroidism at a median age of 0.1 years (range 0–14.7 years) and followed for 9.1 ± 5.5 years after diagnosis, 38% developed nephrocalcinosis.[10] Due to this risk, imaging studies are recommended to screen for nephrocalcinosis in patients treated for hypoparathyroidism.[11] However, due to the persistence of the anticalciuric effect of PTH, renal complications may be less likely in PHP and it is unclear if such screening is necessary for individuals with PHP.[3] In this retrospective study, we sought to define the prevalence of nephrocalcinosis in patients with PHP and to determine if radiologic screening is justified.

Methods

This retrospective study was approved by the Indiana University Institutional Review Board and a waiver of consent/assent was provided. A chart review was conducted at our tertiary academic medical center in pediatric and adult patients. Medical records were identified in our clinical billing database by searching for the ICD-9 code 275.49 for clinical encounters from the years 1990–2015. Exclusion criteria included lack of actual PHP diagnosis (coding error) and lack of renal imaging. Data were collected from the electronic medical record and/or paper charts at both the time of diagnosis and at each subsequent visit with renal imaging. Data collected included age, sex, ethnicity, body weight, laboratory results, age at PHP diagnosis, PHP type, age at initial PTH elevation, age at hypocalcemia, presence of TSH resistance (defined as an elevated TSH value with negative thyroid antibodies), presence of documented subcutaneous ossifications, renal imaging results, and calcitriol and

calcium doses at the time of imaging. The presence of nephrocalcinosis was documented from the clinical report of the interpreting pediatric radiologist.

The proportion of patients with individual clinical features were calculated, and the mean ± standard deviation or median (range) for continuous variables are listed. The 95% confidence interval for the proportion of patients having nephrocalcinosis was estimated using the Clopper-Pearson method.

Results

The database contained 36 patients with an ICD-9 code consistent with PHP. Based on review of clinical notes, 4 patients were excluded due to not having PHP. Of the 32 patients with PHP, 19 had at least one available renal imaging study and were included in the analysis. Among these 19 patients, 12 were diagnosed with Albright's Hereditary Osteodystrophy phenotype (PHP Type 1a), 2 were diagnosed with PHP Type 1b, and 5 were not classified as having a specific subtype of PHP.

Patient characteristics are described in Table I. The cohort had a slight female predominance (58%). The median age at diagnosis of PHP was 8.2 years (range 0.3 to 17.5 years). Patients were a median age of 8.2 years (range 0.5 to 17.5 years) at the earliest noted PTH elevation and at a median age of 8.5 years (range 0.5 to 17.4 years) at their earliest documented hypocalcemia. Subcutaneous ossifications were documented in 42% and TSH resistance in 55%.

A total of 49 renal imaging studies were completed in 19 PHP patients. These studies included renal ultrasonography in 15 patients, computed tomography (CT) of the kidneys in one patient, and both renal ultrasonography and CT in 3 patients. The number of studies in a single individual ranged from 1 to 7 with the mean (± SD) number of studies per individual being 2.6 ± 1.8. The median age at the first imaging study was 11.8 years of age (range 1.1 to 32.5 years). The median age at the last imaging study was 14.6 years of age (range 6.1 to 32.5 years). Among patients (n=11) with multiple imaging studies, the interval from the first to last study was a median duration of 8.0 years. Excluding the 1 patient who had a follow-up ultrasound at 3 months (see below), the median duration between first to last studies was 8.5 years (3.2 to 11.4 years)

Only 1 of 19 (5.3%) patients had an imaging study that was "suggestive of mild medullary nephrocalcinosis". However, after a normal follow-up renal ultrasound 3 months later, pediatric radiology reviewed the initial study and re-interpreted it as also being normal without evidence of nephrocalcinosis. Therefore, none of the assessed subjects with PHP had documented nephrocalcinosis (with a 95% confidence interval for the proportion estimate: 0%, 17.65%).

Biochemical data for the cohort at the time of the initial imaging study is noted in Table II. At the time of the initial imaging, 4 patients were on no treatment, 10 patients were taking calcitriol and/or calcium, and treatment information was not available for the remaining 5 patients. Doses were available in 8 of the patients taking calcitriol (median 12.9 ng/kg/day) and 6 of the patients taking calcium (median elemental calcium 25.0 mg/kg/day). Mean

calcium and phosphate levels were 7.9 ± 1.3 mg/dL and 6.7 ± 1.7 mg/dL, respectively, the majority of which were obtained within a month of the renal imaging studies (n=16). The mean urine calcium/creatinine ratio was 0.04 ± 0.02 mg/mg (n=8).

Biochemical data for the cohort at the time of the initial and subsequent imaging studies are described in Table II. The median calcitriol (8.9 ng/kg/day) and calcium (18.7 mg/kg/day elemental) doses declined from the doses at the time of initial imaging. The mean calcium and phosphate concentrations were 8.3 ± 1.1 mg/dL and 6.1 ± 1.7 mg/dL. The mean urine calcium/creatinine ratio was similar and low at 0.04 ± 0.04 mg/mg (9 patients, 17 samples).

Discussion

We demonstrate the absence of nephrocalcinosis in a clinical cohort of subjects with PHP.[3] There were no cases of nephrocalcinosis detected in 49 imaging studies amongst 19 patients with PHP followed to a median age of 14.6 years (range 6.1 to 32.5 years). This confirms the assertions of multiple authors that these patients should not be expected to be at high risk for nephrocalcinosis based on data from animal models including the tissue specific imprinting of *GNAS* and the persistent anticalciuric effect of PTH in PHP[6, 12].

$G_s\alpha$ is predominately expressed from the maternal allele in the proximal renal tubules, pituitary gland, gonads and thyroid gland, while most tissues have biallelic expression including the skeleton and the distal renal tubule. Mouse models having either maternal or paternal inheritance of a null allele of the mouse homolog *Gnas* confirm that PTH resistance occurs in mice with the maternal null allele, but not in mice with the paternal null allele, recapitulating the human phenotype.[7, 13] $G_s\alpha$ in the renal cortex is markedly reduced in maternal null but not in paternal null mice, while in the renal inner medulla the response to hormones using the G_s-coupled pathway (including PTH and vasopressin) is normal in both models.[7] These models confirm that PTH resistance occurs in the proximal tubule but not the distal tubule in PHP.

Patients with hypoparathyroidism taking calcitriol and calcium supplements lack the normal feedback mechanism to decrease PTH (and hence activated vitamin D), and therefore, serum calcium levels can be driven too high by treatment. Even at normal calcium concentrations, there is increased renal calcium throughput during treatment. Resultant hypercalciuria presents a clinical risk for developing nephrocalcinosis.[14] At a mean age of 11 ± 5.9 years, 38% of children with hypoparathyroidism had developed nephrocalcinosis.[10]

In contrast, in PHP with persistent distal tubule responsiveness to PTH, the kidney should be protected from excessive calcium throughput at low or normal serum calcium levels as compared with hypoparathyroid patients. Litvak et al noted that hypocalcemic hypercalciuria occurred during treatment of patients with hypoparathyroidism, but not in 6 patients with PHP.[15] However, PHP patients may still be at risk for hypercalciuria and nephrocalcinosis if they are over treated with calcitriol and calcium, especially if hypercalcemic. If calcium and calcitriol intake is too high, persons with PHP may see an appropriate decline in PTH below normal levels (as expected for normal individuals). Accordingly, an intravenous calcium infusion leading to transient hypercalcemia does decrease the PTH appropriately in PHP.[16]

Therefore, monitoring PTH concentrations may be important to identify whether calcium or calcitriol doses are excessive in PHP (even in the absence of hypercalcemia or hypercalciuria). PTH is elevated in untreated patients with PHP and often remains elevated during treatment. The skeleton maintains responsiveness to elevated PTH levels in PHP, which might increase the risk of osteoporosis and skeletal fragility over a lifetime. In addition, development of tertiary (hypercalcemic) hyperparathyroidism has been reported in several patients with PHP.[17] Inverse relationships between PTH and bone mineral density were detected in some studies in PHP1b but not in PHP1a.[18, 19] However, because bone effects may be possible, some experts have recommended treating with enough calcium and calcitriol to normalize the elevated PTH in patients with PHP.[20, 21] Unfortunately, PTH was not routinely monitored during therapy of our patients in this retrospective study, so we are unable to evaluate the effects of a treatment strategy targeting normalized PTH. However, we expect that normalizing PTH would likely be safe in these patients, while suppressed PTH levels would indicate excessive calcium intake and absorption, just as it would in a generally healthy population.

Although our study cannot test or confirm the treatment targets, we recommend targeting normal serum PTH, calcium and phosphorus levels as likely being safe and monitoring urine calcium excretion for signs of excessive treatment. No consensus exists regarding the frequency of PTH monitoring in PHP.

It would be reasonable to check serum calcium, creatinine and phosphorus every 3 months, and PTH levels every 6 months with a concurrent serum calcium and urine calcium/creatinine ratio. However, more frequent monitoring of serum calcium and phosphorus are recommended when titrating doses, or based on symptoms of hypocalcemia or hypercalcemia.

This study is limited by a small sample size and retrospective nature in a rare disease. Because this was a chart review, rather than a prospective study, we are limited by access to clinical notes and study reports, and the way individual physicians record data on various clinical features and medication doses, along with an inability to standardize laboratory measurements and imaging assessment intervals. Biochemistries were not collected in conjunction with each imaging study and not always in a uniform manner. PTH levels were not routinely measured during treatment in this cohort. Additionally, only the doses of elemental calcium and calcitriol that could be clearly ascertained from the accessible medical record were reported in this study. For some patients, doses could not be identified, and compliance with treatment in general could not be determined. Some patients with PHP did not have identifiable imaging reports for inclusion, which could have underestimated the prevalence of nephrocalcinosis. In addition, because there were no cases of nephrocalcinosis, we are unable to assess whether particular clinical variables would represent higher risk in patients with PHP. However, strengths include the assessment of multiple imaging assessments in a relatively large cohort of patients with this rare disease. The confidence intervals of the proportions suggest we are unlikely to have missed a “true” prevalence over 17.65%, which is much lower than the reported prevalence of nephrocalcinosis in hypoparathyroidism (38%).[10] Future studies would require pooling data

from multiple centers to create larger cohorts with longer duration of monitoring to confirm these findings.

Recommendations on renal imaging in PHP patients are discrepant with some papers recommending surveillance for patients with PHP (often combined with recommendations for hypoparathyroidism),[22, 23] although others suggest that PHP patients are at low risk for nephrocalcinosis.[3] This data, combined with the current understanding of PHP pathophysiology, suggests that the risk for nephrocalcinosis development during childhood is low, unless the serum calcium concentration or urine calcium excretion becomes elevated, or the PTH concentration becomes suppressed.

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Abbreviations

AHO	Albright hereditary osteodystrophy
$G_s\alpha$	α subunit of the stimulatory G protein
PHP	Pseudohypoparathyroidism
PTH	Parathyroid hormone
TSH	Thyroid stimulation hormone

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Table 1

Patient characteristics

	N=19
Gender - Female	58%
Age at PHP diagnosis, median (range)	8.2 (0.3–17.5)
Age at first hypocalcemia observation, median (range)	8.8 (0.5–17.4)
Age at first elevated PTH observation, median (range)	8.2 (0.5–17.5)
Subcutaneous ossifications	42%
TSH resistance	58%
Imaging assessments, median (range)	2 (1–7)
Years of follow-up, median (range)	7.1 (0.0–27.0)
Age (years) at first renal imaging study, median (range)	11.8 (1.1–32.5)
Age in (years) at last renal imaging study, median (range)	14.6 (6.1–32.5)

Table 2

Biochemical and treatment data

	Data at time of initial imaging	n	Data across all imaging studies	n[a]	Normal range	Age for normal range
Calcitriol dose (ng/kg/day), median (range)	12.9 (5.2–37)	8	8.9 (1.8–37)	17		
Elemental calcium (mg/kg/day), median (range)	25.0 (8.7–103.4)	6	18.7 (8.7–103.4)	10		
Serum Calcium, mean (SD) mg/dL	7.9 (1.3)	16	8.3 (1.1)	35	8.5–10.5 mg/dL	
Serum Creatinine, mean (SD) mg/dL	0.57 (0.14)	6	0.6(0.1)	11	0.4–1.0 mg/dL	
Serum Phosphorus, mean (SD) mg/dL	6.7 (1.7)	16	6.1 (1.7)	35		
	8.1 (1.2)	2	8.1 (1.2)	2	3.6–6.5 mg/dL	1–5 years
	7.5 (1.4)	3	7.6 (1.4)	5	3.4–5.5 mg/dL	5–10 years
	6.4 (1.7)	10	5.9 (1.4)	26	2.6–5.2 mg/dL	10–20 years
	5.2 (0)	1	4.1 (1.2)	2	2.5–4.9 mg/dL	>20 years
Urine calcium/creatinine ratio, mean (SD) mg/mg	0.04 (0.02)	8	0.04 (0.04)	17		
	0.17 (0)	1	0.17 (0)	1	<0.28 mg/mg	19 month –6 years
	0.04 (0.01)	7	0.05 (0.04)	16	<0.20 mg/mg	>6 years

[a]Some of the subjects had multiple samples during follow-up, leading to n>19 in some cases