Prevalence of Nephrocalcinosis in Pseudohypoparathyroidism: Is Screening Necessary?

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The prevalence of nephrocalcinosis in persons with pseudohypoparathyroidism has not been systematically examined. We conducted a retrospective study of renal imaging and biochemical results in 19 patients with pseudohypoparathyroidism with 49 imaging assessments. No cases of nephrocalcinosis were identified. Routine screening for nephrocalcinosis in pseudohypoparathyroidism may not be necessary. *(J Pediatr 2018;■■:■■-■■).*

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 adenosine monophosphate 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 phenotype (stocky build, short stature, round facies, brachydactyly, and variable intellectual disability).[4,5] Various subtypes of PHP have been described. Some individuals may have resistance to additional hormones, such as thyroid-stimulating hormone (TSH), 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 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 D_3 (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 with hypoparathyroidism, individuals with PHP develop elevated PTH concentrations owing 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 D_3, whereas the distal tubule maintains its anticalciuric response to PTH. Clinical evidence of PTH resistance develops over time with increased 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 with regard 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; hypercalciuria is common. Consequently, out of 29 children diagnosed with hypoparathyroidism at a median age of 0.1 years (range, 0.0-14.7 years) and followed for 9.1 ± 5.5 years after diagnosis, 38% developed nephrocalcinosis.[10] Owing to this risk, imaging studies are recommended to screen for nephrocalcinosis in patients treated for hypoparathyroidism.[11] However, owing 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 *International Classification of Diseases*-9 code 275.49 for clinical encounters from the years 1990-2015. Exclusion criteria included lack of actual PHP

$G_s\alpha$	α subunit of the stimulatory G protein
PHP	Pseudohypoparathyroidism
PTH	Parathyroid hormone
TSH	Thyroid-stimulating hormone

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Table I. Patient characteristics

Characteristics	n = 19
Sex (female)	58%
Age at PHP diagnosis	8.2 (0.3-17.5)
Age at first hypocalcemia observation	8.8 (0.5-17.4)
Age at first elevated PTH observation	8.2 (0.5-17.5)
Subcutaneous ossifications	42%
TSH resistance	58%
Imaging assessments	2 (1-7)
Years of follow-up	7.1 (0.0-27.0)
Age (y) at first renal imaging study	11.8 (1.1-32.5)
Age (y) at last renal imaging study	14.6 (6.1-32.5)

Data are median (range) unless otherwise noted.

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 increased 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 ± SD or median (range) for continuous variables are listed. The 95% CI for the proportion of patients having nephrocalcinosis was estimated using the Clopper-Pearson method.

Results

The database contained 36 patients with an *International Classification of Diseases*-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 1 available renal imaging study and were included in the analysis. Among these 19 patients, 12 were diagnosed with Albright 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, 0.3-17.5 years). Patients were a median age of 8.2 years (range, 0.5-17.5 years) at the earliest noted PTH elevation and at a median age of 8.5 years (range, 0.5-17.4 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 patients with PHP. These studies included renal ultrasound imaging in 15 patients, computed tomography of the kidneys in 1 patient, and both renal ultrasound imgaing and computed tomography 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 of 2.6 ± 1.8. The median age at the first imaging study was 11.8 years of age (range, 1.1-32.5 years). The median age at the last imaging study was 14.6 years of age (range, 6.1-32.5 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 examination at 3 months, the median duration between first to last studies was 8.5 years (range, 3.2-11.4 years)

Only 1 of 19 patients (5.3%) had an imaging study that was "suggestive of mild medullary nephrocalcinosis." However, after a normal follow-up renal ultrasound examination 3 months later, pediatric radiology reviewed the initial study and reinterpreted it as also being normal without evidence of nephrocalcinosis. Therefore, none of the assessed subjects with PHP had documented nephrocalcinosis (with a 95% CI for the proportion estimate of 0.00%-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/

Table II. Biochemical and treatment data

Characteristics	Data at time of initial imaging	n	Data across all imaging studies	n*	Normal range	Age for normal range
Calcitriol dose (ng/kg/d)	12.9 (5.2-37)	8	8.9 (1.8-37)	17		
Elemental calcium (mg/kg/d)	25.0 (8.7-103.4)	6	18.7 (8.7-103.4)	10		
Serum calcium (mg/dL)	7.9 ± 1.3	16	8.3 ± 1.1	35	8.5-10.5	
Serum creatinine (mg/dL)	0.57 ± 0.14	6	0.6 ± 0.1	11	0.4-1.0	
Serum phosphorus (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	1-5 y
	7.5 ± 1.4	3	7.6 ± 1.4	5	3.4-5.5	5-10 y
	6.4 ± 1.7	10	5.9 ± 1.4	26	2.6-5.2	10-20 y
	5.2 ± 0.0	1	4.1 ± 1.2	2	2.5-4.9	>20 y
Urine calcium/creatinine ratio (mg/mg)	0.04 ± 0.02	8	0.04 ± 0.04	17		
	0.17 ± 0.00	1	0.17 ± 0.00	1	<0.28	19 mo-6 y
	0.04 ± 0.01	7	0.05 ± 0.04	16	<0.20	>6 y

Values are median (range) or mean ± SD.
*Some of the subjects had multiple samples during follow-up, leading to n > 19 in some cases.

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