

Understanding and Recognizing Pseudohypoparathyroidism

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In Brief

Understanding and Recognizing Pseudohypoparathyroidism

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Hypoparathyroidism and Mineral

- Homeostasis. Perheentupa J. In: Lifshitz F, ed. *Pediatric Endocrinology*. 3rd ed. New York, NY: Marcel Dekker, Inc; 1996:433–471
- Parathyroid Hormone Resistance Syndromes. Levine MA. In: Favus MJ, ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1999: 230–235
- An Example of Seabright-Bantam Syndrome. Albright F, Burnett CH, Smith PH. *Endocrinology*. 1942;30; 922–932

Pseudohypoparathyroidism (PHP) refers to a heterogeneous group of disorders characterized by target organ (bone and kidney) resistance to parathyroid hormone (PTH). In all its forms, PHP is characterized by hypocalcemia, hyperphosphatemia, and supranormal plasma concentrations of PTH. Fuller Albright first suggested hormone resistance as the mechanism of disease in his 1942 report of several patients who apparently had biochemical hypoparathyroidism. These patients failed to respond to an injection of parathyroid extract with the expected rise in serum calcium and phosphate diuresis. Albright also was struck by the skeletal and developmental abnormalities common to many patients who had PHP. This constellation of physical findings, now called Albright hereditary osteodystrophy (AHO), includes: stocky or obese body habitus; moon-shaped face; hypoplasia of the dental enamel; joint deformities (genu valgum, coxa vara, cubitus valgus); and anomalies of the hands and feet, particularly short metacarpal and metatarsal bones of the fourth and fifth digits. Some 50% to 75% of patients also have mild-tomoderate mental retardation. AHO often is not recognizable in the first postnatal year, becoming more apparent at 4 to 6 years of age.

With further clinical experience, it became evident that PHP and AHO are not synonymous. Not all PHP patients have the AHO phenotype, and some AHO patients do not have PHP. Historically, patients who had AHO and were not resistant to PTH were labeled as having "pseudo-pseudohypoparathyroidism." This confusing term has been replaced; AHO now is used to identify the physical syndrome without regard to the biochemistry.

PHP has been classified into several types, depending on clinical appearance, biochemical parameters, and the underlying molecular mechanism of hormone resistance (Table). The most common form of PHP is type Ia, an autosomal dominant disorder that has AHO features. PTH resistance results from a mutation in the *GNAS1* gene, which encodes a subunit of guanine nucleotide binding protein. This protein is the key transducing signal in a variety of endocrine target tissues, explaining why many patients who have PHP Ia exhibit resistance to other hormones besides PTH, most commonly to thyrotropin-stimulating hormone (TSH) and the gonadotropins. Clinically indistinguishable from primary hypothyroidism, TSH resistance may become apparent before hypocalcemia develops and, occasionally, is diagnosed through newborn screening. Hypogonadism is more common in females and may present with sexual immaturity, menstrual cycle abnormalities, and infertility. Whether hormone resistance is expressed at all depends on genetic imprinting. In maternally transmitted GNAS1 defect, hormone resistance is expressed along with the AHO phenotype; in paternal imprinting, the AHO phenotype occurs in isolation.

For unknown reasons, most patients who have PHP type Ia have normal calcium concentrations for many years, rarely demonstrating low serum values before 3 years of age. Although tetany and grand mal seizures are common presentations of hypocalcemia in school-age children who have PHP la, some patients remain asymptomatic until adulthood. Another clinical manifestation of PHP type la is ossified subcutaneous nodules. Radiographically, there may be evidence of progressive calcification of the basal ganglia, but these calcifications are not responsible for the mental retardation of the patients.

Type Ib, the second most common form of PHP, can be either familial or sporadic. PTH resistance does not result from a *GNAS1* gene mutation because guanine nucleotide binding protein has normal activity. With a normal GNAS1 genotype, affected patients have no features suggestive of AHO, either in appearance or cognitively. Hormonal resistance is limited largely to PTH tar-

| РНР Туре | AHO Phenotype | Resistance | Response to PTH | Mechanism | |
|---|---------------|------------|-----------------|------------------------------------|--|
| la | Yes | Yes | Decreased | GNAS1 mutation | |
| AHO (Pseudo-PHP) | Yes | No | Normal | GNAS1 mutation | |
| lb | No | No | Decreased | Regulation defect of PTH receptor | |
| lc | Yes | Yes | Decreased | GNAS1 normal | |
| 1 | No | No | Normal | Acquired defect, unclear mechanism | |
| | | | | | |
| PHP=pseudohypoparathyroidism; AHO=Albright hereditary osteodystrophy; PTH=parathyroid hormone | | | | | |
| | | | | | |

Nephrogenic cAMP

Table. Differentiating Among the Types of Pseudohypoparathyroidism

Other Hormone

get tissues in the kidney, possibly from a defect in regulation of the PTH receptor. Biochemically, type Ib is similar to type Ia, with a very high concentration of PTH, low serum calcium and high serum phosphorous values, and a blunted increase of nephrogenous cAMP in response to intravenous PTH injection. Interestingly, patients who have PHP type Ib demonstrate osteitis fibrosa cystica more frequently, which is characteristic of high bone turnover from PTH overstimulation. This finding implies that skeletal PTH resistance in PHP type lb is not as complete as in type la, in which such skeletal lesions rarely are present.

The small group of patients who have type Ic have the AHO phenotype and multiple hormonal resistance, as in type Ia, but they have normal guanine nucleotide binding protein activity. Currently, the mechanism underlying their defect in transduction signaling has not been identified.

Patients who have PHP type II appear normal (no GNAS1 defect) and demonstrate target tissue resistance only to PTH. Urinary cAMP concentrations increase appropriately with PTH administration, indicating that the PTH-receptor-cAMP complex functions normally. However, there is no appropriate phosphaturic response to PTH, suggesting that resistance most likely arises from the inability of the cAMP to activate downstream targets. With no clear pattern of inheritance and a variable age of onset (ranging from infancy to old age), PHP type II may be an acquired condition.

Every person who has the AHO phenotype and typical constellation of laboratory results (low calcium, elevated phosphate, and elevated or high normal PTH values) should be evaluated for PHP type Ia. For patients who have normal physical appearances and intelligence, the response to a PTH stimulation test differentiates PHP type lb from type II, which have the same phenotypes and biochemical profiles. Secondary causes of hyperparathyroidism may mimic PHP. Renal failure can be ruled out easily with normal serum creatinine and blood urea nitrogen findings. Hypomagnesemia and severe vitamin D deficiency should be excluded because both reduce end-organ responsiveness to PTH. An elevated PTH concentration

differentiates PHP from "true" hypoparathyroidism, as seen in the DiGeorge syndrome, where a microdeletion in chromosome 22 results in aplastic or hypoplastic parathyroid glands.

For patients who have PHP, the lack of response to PTH results in inadequate renal production of 1,25dihydroxyvitamin D (calcitriol) that, in turn, reduces intestinal calcium absorption and contributes to hypocalcemia. Treatment with calcitriol bypasses the enzymatic block and, when coupled with dietary calcium supplementation, can achieve normocalcemia. The most serious risk of therapy is overcorrection, leading to unnoticed hypercalciuria, irreparable kidney damage, and hypercalcemia. Patients treated with vitamin D and its analogs must be followed closely to avoid these complications. Serum phosphate values usually normalize with calcium and calcitriol supplementation; phosphate-binding gels rarely are needed. Patients who have PHP la may require hormone replacement therapy for clinical hypothyroidism and hypogonadism due to hormone resistance.

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