Pseudohypoparathyroidism

Background

Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders characterized by Hypocalcemia, hyperphosphatemia, increased serum concentration of parathyroid hormone (PTH), and insensitivity to the biological activity of PTH.

In 1942, Fuller Albright first introduced the term pseudohypoparathyroidism to describe patients who presented with PTH-resistant hypocalcemia and hyperphosphatemia along with an unusual constellation of developmental and skeletal defects, collectively termed Albright hereditary osteodystrophy (AHO). These features include short stature, rounded face, shortened fourth metacarpals and other bones of the hand and feet, obesity, dental hypoplasia, and soft tissue calcifications/ossifications. In addition, administration of PTH failed to produce the expected phosphaturia or to stimulate renal production of cyclic adenosine monophosphate (cAMP).

Pathophysiology

Several variants of PHP have been identified, and PHP type 1a is the best understood form of the disease. The molecular defects in the gene (*GNAS1*) encoding the alpha subunit of the stimulatory G protein (Gsa) contribute to at least 3 different forms of the disease: PHP type 1a, PHP type 1b, and pseudopseudohypoparathyroidism (pseudo-PHP).

All patients are heterozygous, with one normal Gsa allele; the mutant allele leads to production of inactive Gsa or to small amounts of active Gsa. Several other peptide hormones, including thyrotropin, antidiuretic hormone, the gonadotropins, glucagons, adrenocorticotropin, and growth hormone–releasing hormone, use the alpha subunit of stimulatory G protein to enhance cAMP production. Patients with PHP type 1a can present with resistance to the effects of any of these hormones, although in most patients, responses to corticotropin and glucagon are clinically unaffected.

The dominant pattern of inheritance of PHP type 1a has been attributed to haploinsufficiency of *GNAS1,* meaning that the protein produced by a single normal Gsa allele cannot support normal function, although it may suffice for survival. The single normal Gsa allele preserves the responses to hormones such as corticotropin and glucagon. The haploinsufficiency of the *GNAS1* gene is tissue specific, which may explain the selective resistance to hormones and the characteristic habitus of patients with PHP type 1a.

In the same family, some patients with a defective *GNAS1* gene have resistance to PTH, whereas others share with them the habitus of AHO but are not resistant to PTH. The latter group are said to have pseudo-PHP. In a 1993 report, Davies et al reported an analysis of pedigrees of families that included patients with PHP and pseudo-PHP, suggesting that patients who

inherit the defective gene from the father have pseudo-PHP because the mutant gene is not expressed and the product of a single maternally inherited *GNAS1* gene preserves normal responses to PTH and thyrotropin. However, the occurrence of AHO in patients with pseudo-PHP indicates that one *GNAS1* gene is not sufficient in all tissues.

Patients with PHP type 1b have a genetically and biochemically distinct disorder. Patients with PHP type 1b lack features of AHO, have normal expression of Gsa protein in accessible tissues, and manifest hormonal resistance limited to PTH target tissues. PTH resistance may be limited to the kidney, with PTH responsiveness preserved in the bone, as evidenced by the hyperparathyroid skeletal lesions observed in these patients.

This disorder is inherited as an autosomal dominant trait, but mutations have not been found in the PTH gene or PTH receptor genes. In 1998, Juppner et al reported a study that involved 4 kindreds with affected members; the unknown gene was paternally imprinted and was mapped to a small region of band 20q13.3, very near the *GNAS1* gene.

The severity of PHP type 1b can vary considerably from one patient to another; even within single kindred, the different affected members may experience considerable variations in the severity of the disorder. Members of the affected family who share the same haplotype in band 20q13.3 have been reported to be clinically asymptomatic and to have serum calcium levels within the reference range.

Current data suggest that a molecular defect in the *GNAS1* gene may also be responsible for at least some forms of PHP type 1b. A mutant promoter or enhancer region of the *GNAS1* gene that has lost the ability to support expression of Gsa in the kidney but not in other tissues may be responsible for the renal resistance to PTH. Interestingly, a 2001 publication by Wu et al reported identification of a novel mutation in the carboxyl terminus of the *GNAS1* gene in 3 patients with PHP type 1b and their clinically unaffected mother and maternal grandfather.[2] The absence of PTH resistance in the mother and maternal grandfather who carry the same mutation is consistent with current models of paternal imprinting of the *GNAS1* gene.

Testotoxicosis with PHP type 1a can occur. Gonadotropin-independent sexual precocity has been reported in 2 boys who presented in infancy with classic PHP type 1a. Usually, patients with PHP type 1a show resistance to luteinizing hormone, which could lead to primary testicular insufficiency. The paradoxical presentation of testotoxicosis in these boys resulted from an identical point mutation in the *GNAS1* gene, which caused both a loss and gain of Gsa function. PHP type 1a, characterized by a loss of Gsa function, is caused by thermal inactivation of the mutant protein at body temperature. Testotoxicosis indicates an organ-specific gain of Gsa function, resulting from the expression of the mutant protein. The lower temperature of the testes protects the mutant protein from thermal inactivation.

Two other variants of PHP, PHP type 1c and PHP type 2, are much less characterized than the other forms of PHP. Patients with PHP type 1c do not have a detectable defect in Gsa protein despite having clinical and laboratory findings similar to those observed in patients with PHP type 1a. Patients with PHP type 2 shows no skeletal and developmental defects, similar to patients with PHP type 1b, but they show a normal urinary cAMP response, in contrast to patients with PHP type 1b.

Patients with PHP can present in infancy, especially if significant Hypocalcemia occurs. Some forms of PHP may remain unnoticed or undiagnosed if patients do not have Hypocalcemia and/or features of AHO.

An interesting association between PHP type 1a and hypercalcitoninemia without any evidence of medullary thyroid carcinoma has been described.

There are case reports of vitamin D deficiency mimicking PHP. The clinical presentation and biochemical features of stage 1 vitamin D deficiency rickets (VDR) and pseudohypoparathyroidism type 2 are quite similar.

In a 2005 report, Mahmud et al describe 2 sisters who were initially identified as having paroxysmal dyskinesia, but who, on subsequent testing, showed hypocalcemia, hyperphosphatemia, and elevated PTH levels consistent with PHP type 1b.[3]

Frequency

In 1998, a nationwide epidemiologic survey of PHP was conducted in Japan based on hospital visits in 1997; the period prevalence was 3.4 cases per 1 million people. No information is available regarding prevalence in the rest of the world.

Race

No racial or ethnic differences have been reported.

Sex

PHP occurs approximately twice as frequently in females as in males.

History

- Patients with PHP type 1a present with a characteristic phenotype, collectively called AHO. The constellation of findings includes short stature, stocky habitus, obesity, developmental delay, round face, dental hypoplasia, brachymetacarpals, brachymetatarsals, and soft tissue calcification/ossification.
- Hypocalcemia in children or adolescents is often asymptomatic.
- Patients may develop paresthesias, muscular cramping, tetany, carpopedal spasm, or seizure.

- Patients with PHP type 1a may have disturbances in taste, smell, vision, and hearing, and they may be hyporesponsive to the biological effects of other peptide hormones that use the alpha subunit of the Gsa protein to enhance cAMP production. The hormones under this class include thyrotropin, antidiuretic hormone, the gonadotropins, glucagon, adrenocorticotropin, and growth hormone–releasing hormone. Evaluate patients for signs and symptoms suggestive of deficiencies of any of these hormones.
- Primary hypothyroidism occurs in most patients with PHP type 1a.
- Reproductive dysfunction commonly occurs in persons with PHP type 1a. Women may have delayed puberty, oligomenorrhea, and infertility.
- Features of hypogonadism may be less obvious in men. Testes may show evidence of maturation arrest or may fail to descend normally. Fertility appears to be decreased in men with PHP type 1a.
- Within the spectrum of PHP type 1a, variability exists in osteoclast responsiveness to PTH. Some patients may have osteopenia and rickets.
- Mentation is impaired in approximately half of patients with PHP type 1a and appears to be related to the Gsa deficiency rather than to chronic hypocalcemia because patients with other forms of PHP and hypocalcemia have normal mentation.
- Unusual presenting manifestations include neonatal hypothyroidism, Parkinson disease, and spinal cord compression.

Physical Examination

- Physical examination may reveal signs of Hypocalcemia, including positive Chvostek sign (ie, twitching of facial muscles after tapping the facial nerve just in front of the ear) and/or Trousseau sign (ie, carpal spasm after maintaining an arm blood pressure cuff at 20 mm Hg above the patient's systolic blood pressure for 3 min). Occasionally, cataracts or papilledema are present.
- Obesity is a common feature of AHO.
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    - Brachydactyly is the most reliable sign in the diagnosis of AHO. It may be symmetrical or asymmetrical and may involve one or both hands or feet. Shortening of the metacarpals causes shortening of the digits, particularly the fourth and fifth digits. Shortening of the metacarpals may be recognized during physical examination as dimpling over the knuckles of a clenched fist (ie, Archibald sign). Shortening of the distal phalanx of the thumb is evident as a thumb in which the ratio of the width of the nail to its length is increased (ie, so-called murderer's thumb or potter's thumb).
    - Several other skeletal deformities have been described in AHO, including short ulna, bowed radius, deformed elbow, or cubitus valgus and coxa vara, coxa valga, genu varum, and genu valgum deformities.

- Patients with pseudo-PHP have the phenotype of AHO but with normal biochemical parameters. Patients with pseudo-PHP are often found in the same kindreds as those with PHP type 1a.
- Patients with PHP type 1b present with hypocalcemia without AHO. The severity of hypocalcemia can vary greatly among family members of the same kindred.

Causes

Molecular defects in the *GNAS1* gene, which encodes Gsa, contribute to at least 3 different forms of the disease: PHP type 1a, PHP type 1b, and pseudo-PHP.

Lab Studies

- Serum calcium (including measurement of serum total calcium and ionized calcium) to confirm hypocalcemic state: Serum phosphate levels are elevated.
- Determination of the serum concentration of intact PTH by immunoradiometric assay (IRMA): When the serum concentration of PTH in a hypocalcemic patient is increased, the patient has either a form of PHP or secondary hyperparathyroidism.
- Assessment of skeletal and renal responsiveness to PTH: Assessment is accomplished by measurement of changes in serum calcium, phosphorus, cAMP, and calcitriol concentrations and in urinary cAMP and phosphorus excretion after administration of the biosynthetic N-terminal fragment of PTH.
- Consider thyroid function tests and measurement of gonadotropin and testosterone or estrogen levels, in addition to growth hormone function assessed by insulinlike growth factor-1.

Imaging Studies

- Radiography of the hand may show a specific pattern of shortening of the bones in which the distal phalanx of the thumb and the third through fifth metacarpals are shortened most severely. Radiography may also show small soft tissue opacities (calcifications/ossifications).
- CT scanning may reveal calcification of the basal ganglia.

Other Tests

- An electrocardiogram may reveal prolongation of the QT interval secondary to Hypocalcemia.
- Analysis of the *GNAS1* gene helps identify the specific genetic defect in patients with PHP type 1a.
- Patients with PHP type 1b may be evaluated for parathyroid-related bone disease. Consider bone mineral density (BMD) testing in this group of patients.
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Medical Care

All patients with severe symptomatic Hypocalcemia should be initially treated with intravenous calcium. Administration of oral calcium and 1alpha-hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment and should be initiated in every patient with a diagnosis of PHP. The goals of therapy are to maintain serum total and ionized calcium levels within the reference range to avoid hypercalciuria and to suppress PTH levels to normal. This is important because elevated PTH levels in patients with PHP could cause increased bone remodeling and can lead to hyperparathyroid bone disease.

- In adults, infuse approximately 100 mg of elemental calcium (either calcium chloride or calcium gluconate) over 10-20 minutes. If this measure does not alleviate the clinical manifestation, 100 mg/h of elemental calcium can be infused (in adults), with close monitoring of calcium levels. Do not rapidly infuse calcium because of the possible adverse effects of cardiac conduction defects; cardiac monitoring may help guide therapy. The two most readily available formulations for parenteral use are calcium chloride and calcium gluconate; a 10-mL ampule of 10% calcium chloride contains 360 mg of elemental calcium, and a 10-mL ampule of 10% calcium gluconate contains 93 mg of elemental calcium.
- For neonates, infants, and children, the recommended initial dose is 0.5-1 mL/kg of 10% calcium gluconate administered over 5 minutes.

Surgical Care

Rarely, extraskeletal osteomas require surgical removal to relieve pressure symptoms.

Diet

No restrictions are necessary.

Activity

No restrictions are necessary.