Albright hereditary osteodystrophy

Authors: Professor Marie-Laure Kottler[1], Doctor Agnès Linglart and Professor Jean-Claude Carel
Creation Date: March 2002
Update: January 2004

Scientific Editor: Professor Didier Lacombe

[1]Laboratoire de génétique moléculaire, CHU Hôpital Clémenceau, Avenue Georges Clémenceau, 14033 Caen Cedex, France. kottler-ml@chu-caen.fr

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Abstract
Albright hereditary osteodystrophy (AHO) is a syndrome with a wide range of manifestations including short stature, obesity, rounded face, subcutaneous ossifications and characteristic shortening and widening of long bones in the hands and feet (brachydactyly mostly affecting the 4th and 5th rays). Mental retardation was less frequently described. These somatic features are associated with resistance to PTH or parathyroid hormone (a syndrome called pseudohypoparathyroidism type 1a or PHP1a) and to other hormones (thyroid-stimulating hormone or TSH in particular). PHP-1a is characterized by hypoparathyroid manifestations (hypocalcemia, hyperphosphoremia) and elevated PTH levels, indicating resistance to the hormone. Patients show decreased biological activity of the protein Gs in erythrocytes. AHO with Gs deficiency but without hormone resistance is called pseudopseudohypoparathyroidism (PPHP). OHA with hormonal resistance but normal Gs activity is called PHP-1c. PHP without AHO (and with normal levels of Gs biological activity) is generally classified as PHP-1b. AHO with decreased Gs activity is due to heterozygous inactivating mutations of the GNAS1 *gene. This gene encodes the α-subunit of Gs, the heterotrimeric G protein that couples with heptahelical plasma membrane receptors. Whether the patient exhibits resistance to hormones or not is determined by the parental origin of the mutation, a functional maternal GNAS1 allele having a predominant role in preventing hormone resistance.*

Keywords
Short stature, obesity, brachydactyly, PTH/TSH-resistance, subcutaneous ossifications, PHP-1a, PHP-1b, PHP-1c, *GNAS1* gene

Disease name and synonyms

Albright hereditary osteodystrophy (AHO) (OMIM 103580),
Pseudohypoparathyroidism type 1a (PHP-1a),
Pseudopseudohypoparathyroidism (PPHP),
Pseudohypoparathyroidism type 1c (PHP-1c).

Excluded diseases

Hypoparathyroidism (lack of parathyroid hormone (PTH) provokes inappropriately low calcium levels).
Pseudohypoparathyroidism type 2 where the defective renal response to PTH is downstream

of the generation of cyclic adenosine monophosphate or cAMP by the tubule.

Diagnosis criteria

Clinical criteria

The clinical description of the dysmorphic syndrome includes obesity, rounded face, and brachydactyly mostly affecting the 4th and 5th rays. Actually, many patients diagnosed with this condition have unremarkable phenotypic features.

Bone X-rays generally show important clinical criteria: brachydactyly mostly affecting the 4th and 5th rays, narrow lumbar canal, and subcutaneous ossifications.

Some degree of developmental delay is common, but generally mild.

PHP-1a

The usual clinical presentation of PHP is hypocalcemia manifesting itself by neuro-muscular hyperexcitability, cramps, carpo-pedal spasms or seizures. The patients also present with obesity, dysmorphic syndrome, isolated elevation of serum thyroid stimulating TSH (usually without overt hypothyroidism), short stature, pubertal delay or elevated gonadotrophin levels. They can also present with subcutaneous ossification.

Biological criteria

PHP-1a

PTH resistance manifests itself by hypocalcemia, hyperphosphoremia with elevated plasma PTH levels. This association with unequivocal clinical criteria or other associated signs of hormonal resistance is sufficient to make a provisional diagnosis of PHP-1a. Additional tests (quantitative analysis of Gs activity, cAMP response to PTH can be useful but is to be performed under specialized supervision).

TSH resistance manifests itself by elevated TSH with normal or low levels of fT4 (free thyroxine) and fT3 (free triiodothyronine).

Gonadotrophin resistance manifests itself by elevated levels of FSH (follicle-stimulating hormone) and LH (luteinizing hormone), generally observed after the onset of puberty. The impact of gonadotrophin resistance on menstrual cycles and on fertility is generally moderate but has not been fully evaluated.

Other biological features include elevated calcitonin levels, blunted cortisol response to ACTH (adrenocorticotropic hormone).

Quantitative analysis of Gsα protein biological activity

PHP-1a

Since Gs protein is present in the membrane of erythrocytes, the absence of Gs in turkey erythrocytes allows this cyc- functional complementation assay. Erythrocytes of patients or controls are used in turkey erythrocyte membranes to generate cAMP. However, this test is not widely available and false positive results (abnormal Gs activity without GNAS1 lesions) can be observed when vitamin D levels are low and false negative results (normal Gs activity with GNAS1 lesion) can be observed when the genetic lesions involve the C-terminus. This condition (AHO, hormonal resistance and normal Gs biological activity) is called PHP-1c.

Molecular findings

Mutations of *GNAS1* are distributed along the coding sequence with however a mutational hot-spot in exon 7 involving codons 189-190 (deletion of 4bp). Exon 1 remains difficult to study because of a high CG content. Most patients (82% in our series) with typical PHP-1a features have detectable heterozygous mutations in *GNAS1*.

A defect in Gsα receptor coupling associated with mutations in the C-terminal region was recently described in some patients with PHP-1c.

Prevalence

OHA is considered as a rare disease. Prevalence of PHP-1a has been estimated to 7.2 per million in Japan, which would be equivalent to approximately 400 cases in France. However, it is believed to be an underestimate.

Clinical description

See diagnosis criteria.

Inheritance

OHA is transmitted as an autosomal dominant trait. However hormone resistance and in particular resistance to PTH depends on whether the mutated allele comes from the father or the mother. Within a family, some patients have isolated features of OHA without hormone resistance (it is called pseudopseudohypoparathyroidism or PPHP) and some show the complete clinical picture described above. This is due to the parental imprinting of the *GNAS1* gene. Thus in individuals with a mutated maternal *GNAS1* allele, the disease is fully expressed while in individuals with a mutated paternal allele the disease is partially expressed and they do not display hormonal resistance (PPHP).

Genetic lesions of *GNAS1* have only been found in PPHP patients relatives to PHP1a patients and not in individuals with apparently sporadic PPHP.

Etiology

In PHP-1a, the molecular defect has been shown to be located in the gene *GNAS1* encoding the Gs α–sub-unit and loss of functional mutations was described in typical PHP1a phenotypes. Mutations are scattered along the gene. Gs is involved in signal transduction of several extra-cellular messengers which interact with 7 transmembrane domain receptors. The protein Gs alpha (Gsα) is one of the subunits of Gs, inducing the stimulation of adenylyl cyclase (AC) and the production of cAMP as a second messenger. Gsα binds to a guanine nucleotide and confers specificity for receptor and effector coupling. By contrast, gain of functional mutations of the same molecule at amino acid 201 was identified in McCune-Albright syndrome.

GNAS1 is a complex gene spanning 20 kb and composed of 13 exons. It maps to 20q13. Additional exons 1 have been identified driven by specific promoters that are differentially methylated. Two of these alternative transcripts encode different proteins: Xlαs a Golgi-specific isoform of Gsα and NESP55, a neuro-secretory protein.

Imprinting of the GNAS1 is an important mechanism in the variation of phenotypic expression of the mutations. Segregation analysis indicates that mutations inherited from the mother or occurring on the maternal allele are associated with the clinical loss of function and hormonal resistance. On the other hand, a mild phenotype with AHO, absence of hormonal resistance and decreased Gs activity (called pseudopseudohypoparathyroidism), is found when mutations are inherited from the father or occur on the paternal allele.

The precise pathogenesis of AHO in patients with PHP 1a and PPHP is not well understood. It does not seem to be due to PTH resistance.

Treatment

Hypocalcemia is managed by intraveinous calcium in case of acute symptoms and with 1-alpha hydroxylated vitamin D derivatives as a chronic treatment. The two drugs used are alfacalcidiol (0.25 μg and 1 μg capsules, 0.1 μg/drop solution) and calcitriol (0.25 μg capsules). The usual dose of alfacalcidiol ranges from 0.5 to 4 μg/day. The usual dose of calcitriol ranges from 0.25 to 2 μg/day. Monitoring should allow adjustment of the drug dose based on plasma calcium and urinary calcium, in order to avoid hypercalciuria. In the long term, bone mass and PTH levels should be monitored, although bone mass does not seem to be compromised in PHP-1a. In PHP-1a, the other aspects of hormone resistance should be evaluated and managed appropriately (resistance to TSH in particular). Follow-up should be comprehensive, given the many manifestations of the disease (overweight, orthopedic aspects).

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