

Acknowledgments

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Clinical and radiological findings in a case of pseudohypoparathyroidism type 1a: Albright hereditary osteodystrophy[☆]



Aspectos clínico-radiológicos en un caso de pseudohipoparatiroidismo tipo 1a: Osteodistrofia hereditaria de Albright

Dear Editor,

Pseudohypoparathyroidism (PHP) comprises a heterogeneous group of diseases characterised by insensibility of target organs to the activity of parathyroid hormone (PTH) resulting from abnormalities in the PTH receptor, either in the alpha subunit of the stimulatory G protein or in the second messenger system.¹ The 2 main subtypes of PHP (1a and 1b) are due to inactivating mutations in the *GNAS* gene

(20q13.2) that encodes the alpha subunit of stimulatory G protein (Gs α).

The patient was a 13-year-old female with subcutaneous nodules in arms and abdomen, lifelong short stature and intellectual disability.

Both parents (Ecuadorian in origin) were healthy. The height of the mother was 151.5 cm and the father's height was 160 cm. There was no perinatal or pathological history of interest. The patient experienced menarche at 11 years of age.

Physical examination: height, 143.7 cm (−2.2 SDS); weight, 55.2 kg; and BMI, 26.7 kg/m² (+2.5 SDS). The patient had a singular phenotype (Fig. 1) with a rounded face, short neck, and shortening of the first toe in both feet as well as of the fourth metacarpal and metatarsal bones in both hands and feet, respectively. Hard subcutaneous nodules 15 mm in diameter were found in the radial side of the forearm, another measuring 5 mm in the hypogastric region, and another measuring 15 mm in the palm of the hand. Palpation revealed an osseous plaque 10 mm in diameter (osteoma cutis) in the right parietal region. The patient had mild intellectual disability and had completed pubertal development.

Laboratory findings included hypocalcaemia, hyperphosphoraemia and elevated PTH. Thyroid function tests, insulin-like growth factor I (IGF-I), prolactin and gonadotropin levels were all normal.

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Figure 1 (A) Clinical characteristics of the patient. (B) Closeup of the hands. (C) Closeup of the feet.

The serial bone X-rays revealed abnormalities in the upper extremities with heavy bones and shortening of the forearms. The patient had carpal bone abnormalities, with pattern of dysplasia in the 5th metacarpal bone (Fig. 2). CT showed calcifications in the basal ganglia. The ophthalmological exam found cortical lenticular cataracts. The patient had a normal female karyotype.

Genetic testing confirmed the diagnosis with the detection of a heterozygous mutation in exon 7 of the *GNAS* gene, consisting in the deletion of four nucleotides (c.565_568delGACT), which causes a reading frameshift starting in amino acid 189 that produces a truncated protein (p.D189MfsX14). Genetic testing of the parents showed lack of mutations, so the patient had a *de novo* mutation.

Treatment with 1,25-dihydrocholecalciferol (0.5 µg/day) and calcium (1 g/day) was prescribed, with low adherence at the outset. At 13 years and 6 months of age, the patient was diagnosed with primary hypothyroidism (TSH 8.86 mIU/mL [0.36–5.5] and free T4 0.6 ng/dL [0.65–1.4]) and was treated with levothyroxine (50 µg/day). The patient is currently 17 years and 10 months of age (height at –2.9 SDS; BMI at +4.9 SDS).

Pseudohypoparathyroidism 1a is caused by inactivating mutations in the maternal allele of the *GNAS* gene that encodes $G_{s\alpha}$.² When the mutation is located in the paternal allele it results in pseudohypoparathyroidism. These patients have the phenotypic characteristics of Albright hereditary osteodystrophy (AHO) but have normal

biochemical findings. This is because the *GNAS* gene is expressed from the maternal allele in the target tissues for PTH, TSH, LH, FSH (proximal tubules of kidneys, thyroid gland and ovaries), so the protein functions normally when the mutation is located in the paternal allele, which is not expressed in these tissues.³

Albright hereditary osteodystrophy is an entity that comprises heterogeneous clinical findings. The most typical characteristics of the Albright phenotype are brachydactyly, with the literature describing a shortening of the third and fourth metacarpal and metatarsal bones and the distal phalanx of the first toe, along with heterotopic ossifications.⁴ Intramembranous heterotopic ossifications may develop, and are usually restricted to subcutaneous tissues, but they occasionally progress into deep tissues, causing progressive osseous heteroplasia (POH). Lenticular cataracts develop in patients with a long duration of disease that have not received treatment.⁵

The goal of treatment in every type of PHP is to correct hypocalcaemia by administering 1,25-dihydrocholecalciferol (0.01 and 0.1 µg/kg/day) and calcium supplementation (0.5–1 g/day). The primary objective is to maintain serum calcium levels in the lower range of normality, urinary excretion of calcium below 4 mg/kg/day and the urine calcium to creatinine ratio under 0.2. Even when the calcium level is normal, administration of calcitriol and calcium is recommended to suppress the PTH production and prevent osseous lesions secondary to elevated blood PTH.⁶



Figure 2 (A) Bone abnormalities in the hand. (B) Bone abnormalities in feet. Note metacarpal and metatarsal defects. (C) Cranial CT. Note calcifications in the basal ganglia.

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