Progressive osseous heteroplasia-like heterotopic ossification in a male infant with pseudohypoparathyroidism type Ia: A case report

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Abstract

Pseudohypoparathyroidism (PHP) Ia is a rare condition associated with multiple hormone resistance and the Albright Hereditary Osteodystrophy (AHO) phenotype. Progressive osseous heteroplasia (POH) is characterized by progressive ossifications of dermal, skeletal muscle and deep connective tissue during childhood. Both PHP Ia and POH are caused by heterozygous inactivating mutations in the GNAS gene. Maternal inheritance of a GNAS mutation leads to an AHO phenotype with hormonal resistance (PHP Ia), whereas paternal inheritance leads to an AHO phenotype without the hormonal resistance (pseudopseudo-hypoparathyroidism). Pure POH (no other AHO features) is also caused by a paternal inheritance of GNAS mutations. Mutations that cause PHP Ia when maternally inherited can cause POH when paternally inherited. We present an unusual case of a boy with clinical features of both POH and PHP Ia, and a GNAS inactivating mutation.

Case presentation: The patient was referred at 1 month of age with a “knot on his leg”. Plain radiographs revealed subcutaneous ossifications. PE at age 4 months included: length and weight >95%, a round face, short 4th metacarpals, and extensive subcutaneous ossifications of the lower limbs, buttocks, and back. Studies at age 4 months included an elevated TSH 12.4 mIU/l, free T4 0.86 ng/dl (0.8–2.3), PTH 61 pg/ml (10–65), calcium 9. 8 mg/dl (9.0–11.0), and phosphorus 6. 4 mg/dl (3.8–6.5). By age 16 months, the PTH was elevated at 126 pg/ml. Biopsies of the skin lesions demonstrated osteoma cutis consistent with POH. GNAS analysis revealed a heterozygous deletion in exon 7. The mutation was not detected in either parent.

Discussion: POH and PHP Ia are rare genetic disorders caused by loss of function mutations of the GNAS gene. POH and PHP Ia do not commonly occur in the same individual as they are associated with paternal versus maternal inheritance (imprinting) of an affected GNAS gene. Our patient has evidence of both severe POH and PHP Ia, apparently due to a de novo mutation in GNAS.

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Introduction

Pseudohypoparathyroidism type Ia (PHP Ia) is a rare condition associated with the Albright Hereditary Osteodystrophy (AHO) phenotype and multiple hormone resistance [1]. Features of the AHO phenotype include short stature, stocky build, round facies with a small nose and flat nasal bridge, brachydactyly with fourth and fifth metacarpophalangeal abnormalities, and superficial tissue subcutaneous ossifications. Patients usually have a pleasant nature and developmental delay with lower IQ [2]. Like AHO, progressive osseous heteroplasia (POH), another disorder of ectopic extraskeletal ossification, is characterized by dermal and subcutaneous ossification. However, in POH the bone
formation is more severe, progressing into skeletal muscle and deep connective tissue during childhood [3,4].

Both PHP Ia and POH are caused by inactivating mutations of the gene encoding the alpha subunit of the adenylate cyclase stimulatory G protein (GNAS, formerly called GNAS1) localized to 20q13.2–13.3 [5,6]. Described GNAS mutations are heterozygous and occur in the GNAS-alpha protein-coding exons [7]. GNAS-alpha is imprinted in a tissue-specific manner, with primarily maternal expression in cells of the proximal renal tubules, pituitary gland, thyroid, and gonads. Maternal inheritance of a mutation in GNAS leads to an AHO phenotype with hormonal resistance (PHP Ia), whereas paternal inheritance leads to AHO phenotype without the hormonal resistance (pseudopseudo-hypoparathyroidism) [8]. Pure POH (no other AHO features) is also caused by a paternal inheritance of GNAS mutations [6]. Mutations that cause PHP Ia when maternally inherited can cause POH when paternally inherited [6].

To date, two unrelated female patients with features of both AHO and POH-like heterotopic ossification have been described, one with AHO and POH, and the other with PHP Ia and POH [9]. We present a report of a boy with POH-like heterotopic ossification, an inactivating GNAS mutation, and multiple hormone resistance consistent with PHP Ia.

Case report

The patient, a Caucasian infant, presented at 4 months of age to the Pediatric Endocrinology Clinic at Riley Hospital for Children, Indianapolis for evaluation of cutaneous and subcutaneous ossifications. He was a product of a full term pregnancy. Birth weight was 4630 g (>95th percentile), and birth length was 58.5 cm (>95th percentile). Birth history was complicated by neonatal hypoglycemia, hypocalcemia, hypoxia, and bradycardia. A work-up for sepsis was undertaken, with subsequent administration of intramuscular antibiotics. Some of those injections were administered in his right thigh.

At 1 month of age he returned to his pediatrician with a “knot” at the area of injection on his right thigh. The lesion was erythematous and felt nodular. Over the next several months, the involved area progressed down to his ankle and medially up to his groin. Radiographic evaluation revealed subcutaneous ossifications (Fig. 1). Approximately 2 months after the appearance of the first lesion, a similar one was noticed on the left ankle and on his back. Over the following months, there was a rapid progression in the size of the existing lesions and in the appearance of new ones.

On physical examination at 4 months of age, both length and weight were above the 95th percentile. He had a round face and flat nasal bridge, bilateral short fourth metacarpals with a classic knuckle-dimple sign consistent with AHO phenotype (Fig. 2). His toes were not malformed. Extensive, discolored, dense, plaque-like lesions were noted over his lower extremities, groin, and back. Some lesions were overlying joints and caused angulation and restriction to movement (Fig. 2). Biopsies of the affected areas demonstrated osteoma cutis (Fig. 3). CT scan demonstrated progression of the ossification
into the skeletal muscle consistent with POH-like heterotopic ossification (Fig. 4). He had no history of seizures.

Laboratory evaluation at 4 months of age revealed an elevated TSH of 12.4 mIU/l (0.4–4.2), a normal free T4 of 0.86 ng/dl (0.8–2.3), PTH 61 pg/ml (10–65), calcium 9.8 mg/dl (9.0–11.0), and phosphorus 6.4 mg/dl (3.8–6.5).

DNA sequence analysis of the GNAS gene revealed a heterozygous inactivating mutation (546delC; GenBank Acc # NM000516 for human GNAS cDNA) in exon 7 of GNAS (H.A. Chapman Institute of Medical Genetics, Tulsa, OK). The 1 bp deletion creates a frameshift with predicted truncation of the protein at amino acid 184. Neither the parents nor the two unaffected full siblings demonstrated the mutation.

Thyroid hormone supplementation was started at age 6 months resulting in prompt normalization of TSH. He developed an elevated PTH of 126 pg/ml at 16 months of age. His calcium at that time was 9.7 mg/dl (9.0–11.0 mg/dl) and phosphorus was 6.5 mg/dl (3.8–6.5 mg/dl). Therefore, a diagnosis of POH-like heterotopic ossification and PHP Ia was made based on the clinical and laboratory findings.

Discussion

Pseudohypoparathyroidism (PHP) was first described in 1942 by Dr. Fuller Albright with a report of a patient with stocky build, short stature, round facies, brachydactyly, soft tissue ossifications, and mental retardation [2], a phenotype subsequently known as Albright Hereditary Osteodystrophy (AHO). Albright’s patient also had hypocalcemic seizures and resistance to parathyroid hormone (PTH), thus the condition was termed “pseudohypoparathyroidism” [10].

PHP was subsequently classified based on the presence or absence of the AHO phenotype and resistance to stimulatory hormones such as PTH, TSH, LH, FSH, and/or GHRH. After the discovery of decreased adenylyl cyclase stimulating protein (Gsα) in some patients with PHP in 1980 [11,12], the lack of Gsα bioactivity became a criterion in the classification of PHP. Some forms of the disease are attributable to inactivating mutations of the GNAS (Gsα) gene, located on chromosome 20q13 [7].

POH was distinguished from other disorders of heterotopic ossification and defined as a unique clinical entity in a 1994 report [4]. In their report, Kaplan et al. described two new cases and reviewed five previously published cases of children with infancy onset non-inflammatory osseous heteroplasia with progressive intramembranous ossification of subcutaneous and deep connective tissues. The disorder was associated with normal intelligence and development [13]. POH follows an autosomal dominant mode of inheritance [14,15], however new sporadic cases are also identified [16]. POH can be distinguished from another severe and disabling disorder of heterotopic ossification, fibrodysplasia ossificans progressiva (FOP), by the absence of congenital malformation of the great toes and by the non-inflammatory and unpredictable regional pattern of ossification [16]. The heterotopic ossification is intramembranous in POH rather than endochondral as in FOP. Skin and subcutaneous fat are always spared in FOP [17]. FOP has recently been demonstrated to be caused by a recurrent mutation in the glycine–serine activation domain of activin A type 1 receptor gene, a type 1 receptor for bone morphogenetic protein on chromosome 2q23–24 [18].

Subcutaneous ossification can also be seen as part of the AHO phenotype and PHP Ia. However, even though an intramembranous pattern is characteristic of both POH and AHO, ossifications seen in AHO tend to be less severe than those of POH and are not mobility-limiting. Progressive heterotopic ossification of cutaneous, subcutaneous, and deep connective tissues with the destruction of anatomic planes differentiates POH from subcutaneous ossifications seen in AHO [17], although involvement of deep cutaneous tissues has been infrequently described in patients with AHO [9].

Even though both PHP Ia and POH are caused by the same gene defects, the resultant phenotypes differ markedly. The multiple hormone resistance that is a defining feature of PHP Ia is not generally associated with POH, a difference currently explained by imprinting of the GNAS gene [19]. GNAS is imprinted in a tissue-specific manner, with primarily maternal expression of Gsα in cells of the proximal renal tubules, pituitary gland, thyroid, and gonads [8].
Some rare cases of POH-like heterotopic ossification are maternally derived and might represent a severe form of AHO [20,21]. This may be the case with our patient. Recently, decreased Gs activity has been directly linked to osteogenic differentiation in human mesenchymal cells [22].

The patient presented here is the first male to be described with evidence of both POH-like heterotopic ossification and PHP Ia as a consequence of a de novo missense mutation. Ahmed et al. [23] reported the cases of two affected children of a mother with pseudopseudo-hypoparathyroidism and a GNAS mutation, a daughter with PHP Ia, and a son with POH. Subsequent to the published report, however, the boy developed resistance to PTH, and therefore PHP Ia ([20], Ahmed, personal communication). Both this boy and our patient, therefore, display similar phenotypes with apparent maternal inheritance.

Our understanding of the etiology, molecular and genetic basis, as well as inheritance of these rare conditions has markedly advanced over the past few decades, yet unanswered questions remain. Further investigation of genetic imprinting, gene inheritance, and genotype–phenotype associations of these rare but debilitating disorders will help us better understand the regulation of heterotopic ossification.

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