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GNAS-associated disorders of cutaneous ossification: two different clinical presentations

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Abstract

Progressive osseous heteroplasia (POH) is a rare genetic disorder characterized by dermal ossification during infancy and progressive ossification into deep connective tissue during childhood. POH is at the severe end of a spectrum of *GNAS*-associated ossification disorders that include osteoma cutis and Albright Hereditary Osteodystrophy (AHO). Here we describe two girls who have different clinical presentations that reflect the variable expression of *GNAS*-associated disorders of cutaneous ossification. Each girl had a novel heterozygous inactivating mutation in the *GNAS* gene. One girl had POH limited to the left arm with severe contractures and growth retardation resulting from progressive heterotopic ossification in the deep connective tissues. The other girl had AHO with widespread, superficial heterotopic ossification but with little functional impairment. While there is presently no treatment or prevention for *GNAS*-associated ossification disorders, early diagnosis is important for genetic counselling and for prevention of iatrogenic harm.

Keywords

Progressive osseous heteroplasia (POH); Albright hereditary osteodystrophy (AHO); Fibrodysplasia ossificans progressiva (FOP); Heterotopic ossification; *GNAS*

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Introduction

Progressive osseous heteroplasia (POH) is a rare genetic disorder of mesenchymal differentiation characterized by dermal ossification during infancy with progressive heterotopic ossification of skeletal muscle and deep connective tissue during childhood [1,2]. The first sign of POH is often osteoma cutis at the site of future, deep heterotopic ossification [1,2].

POH can be distinguished from fibrodysplasia ossificans progressiva (FOP), another rare disorder of heterotopic bone formation, by the presence of cutaneous ossification, superficial to deep progression of heterotopic ossification, the mosaic distribution of lesions, the absence of congenital skeletal malformations or inflammatory tumour-like swellings, and the predominance of intramembranous (in contrast to endochondral) ossification [2,3] (Table 1). Importantly, POH can be distinguished from other *GNAS*-associated disorders of heterotopic ossification [osteoma cutis, Albright Hereditary Osteodystrophy (AHO), and pseudohypoparathyroidism type 1a (PHP1a)] by the progression of heterotopic ossification from skin and subcutaneous tissue into skeletal muscle, the absence of a distinctive habitus associated with AHO, and the presence of normal endocrine function respectively [1–4] (Table 1).

In this report we describe two girls, each with a different clinical presentation that reflects the presence of cutaneous ossification in a broad clinical spectrum of *GNAS*-associated pathology [4].

Case Reports

Patient-1

A Dutch girl, now eight years old, was born at 41.5 weeks gestation to non-consanguineous parents after a normal pregnancy and vaginal delivery. There was no family history of heterotopic ossification or skeletal malformations. At eleven days of age, the mother detected a hard cutaneous lesion just above the left elbow. A skin biopsy at one month revealed dermal ossification. There were no other lesions. Laboratory tests at five months of age were all normal including a serum calcium, phosphate, parathyroid hormone (PTH), 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D. Radiographs showed diffuse ossification of the skin but no skeletal malformations.

At eight months of age, the child was obese (height, 62 cm; weight, 9.6 kg.) but was otherwise developing normally. At 2.5 years of age, a linear papular lesion was noted on the left upper limb from the shoulder to the wrist. The skin was hardened and reddish-purple in colour (Fig. 1a). Over time, the lesion progressed into skeletal muscle, limiting range of motion of the thumb, wrist, and elbow.

At eight years of age, the height and weight age-related percentiles were 0.6% and >98% respectively (height 117 cm and weight 32 kg). A radiograph of the left upper limb revealed a characteristic web-like reticular pattern of heterotopic ossification that had spread from the skin to the deep musculature and periosteum, especially on the radial side. New ossifications appeared distal and proximal to the elbow with severe osteopenia in the associated normotopic skeleton of the left upper limb (Fig. 1b).

POH was suspected on the basis of disease progression from skin and subcutaneous tissue into deep skeletal muscle and connective tissue. DNA analysis, showed a c.1107–1108delTG disease-causing inactivating mutation in exon 13 of the *GNAS* gene (Fig. 3). The parents did not carry this mutation.

Patient-2

A Dutch girl, now 18 years old, was born at 37 weeks gestation to non-consanguineous parents after a normal pregnancy and vaginal delivery. There was no family history of heterotopic ossification or skeletal malformations. Development was normal until seven years of age when her mother noticed a hard subcutaneous lesion on her back that was subsequently excised. Histopathologic evaluation revealed an old hematoma with reactive dermal ossification.

We first saw her at nine years of age. During the previous three months, she had developed small, hard cutaneous lesions on the neck, right foot, knee, and ankle. She was healthy and had a normal weight for her age, but was smaller than normal (P -1,6 SD). Her thumbs were short. Laboratory tests were normal including a serum calcium, phosphate, PTH, and 24-hour urine calcium.

At 18 years of age, short thumbs, bilateral short fourth and fifth metacarpals (Fig. 2a) and short fourth metatarsals (Fig. 2b) were noted and confirmed radiographically (Fig. 2c,d). Radiographs also revealed superficial heterotopic ossification near the right ankle and foot. Also notable was her short stature. In addition, she developed a Madelung deformity, a growth disturbance in the volar-ulnar distal radial physis that results in a volar and ulnar tilted distal radial articular surface, volar translation of the hand and wrist, and a dorsally prominent distal ulna, in both radiocarpal joints [9]. The disease had not progressed since age 15.

Osteoma cutis with AHO features and the absence of PHP1a was suspected on the basis of cutaneous and subcutaneous ossification, the presence of short metacarpals and metatarsals, and the absence of hormone resistance. DNA sequence analysis of the *GNAS* gene showed a novel c.355delC disease-causing inactivating mutation in exon 5 (Fig. 3). The parents did not carry this mutation.

Discussion

Progressive osseous heteroplasia (POH) was first characterized by Kaplan as a distinct disorder of heterotopic ossification in 1994 [1]. The clinical presentation of POH can be variable, but is distinguished from other *GNAS* gene disorders by cutaneous ossification that progresses into deeper tissues and by the absence of hormone resistance [1,2,4]. Here, we describe two girls, with different clinical presentations of *GNAS*-associated disorders of cutaneous ossification. The girls had different ages of onset of heterotopic ossification and had different physical limitations due to their disease.

Osteoma cutis most frequently occurs secondary to trauma, infection or surgery [1]. Three *GNAS*-related disorders in which cutaneous ossification occurs in childhood are isolated osteoma cutis, AHO, and PHP1a [4]. POH can be distinguished from these disorders by the progression of heterotopic ossification from skin and subcutaneous tissue into skeletal muscle, by the absence of distinct multiple AHO features, and by the presence of normal endocrine function respectively [4]. The severity and morbidity of POH depends on the location and extent of the heterotopic ossification [2,4,5]. Lesions can form progressively and ramify into extensive, ossified plaques. Extensive ossification of the deep connective tissues results in contractures of affected joints and focal growth retardation of involved limbs, as in patient-1 [1,2,4–6].

POH belongs to a spectrum of disorders that are associated with inactivating mutations in *GNAS* and that are variably associated with cutaneous and subcutaneous ossification [4,5]. Most cases of POH are associated with heterozygous inactivating mutations of the *GNAS*

gene. However, nearly 30 percent of individuals with a clinical diagnosis of POH do not have detectable mutations of *GNAS* [4,5]. The *GNAS* gene encodes a complex array of transcripts including the alpha subunit of the G-stimulatory protein (Gs- α) of adenylyl cyclase [4,5]. *GNAS* mutations in POH can be familial, but most cases are sporadic as in patient-1 [4–7].

Mutations in *GNAS* do not predict a specific disorder, phenotype, or severity of progression within the spectrum of *GNAS*-related disorders [4]. Patient-2 also had osteoma cutis and a *GNAS* inactivating mutation but lacked the deep progressive heterotopic ossification that is the defining clinical feature that separates POH from all other forms of *GNAS*-associated cutaneous ossification. AHO features are associated with mutations in either of the two *GNAS* alleles. However, PHP1a (and associated hormone resistance) is caused by mutations that specifically occur in the maternally inherited *GNAS* allele [4,5]. By contrast, POH is associated with mutations in the paternally inherited *GNAS* allele [3–5]. Although no further investigation was conducted to determine which parental allele carried the mutation, the absence of PHP1a and hormone resistance in our two patients strongly suggests that the mutations in both girls were carried on the paternal allele [4,5]. Further, genetic counselling is important for both girls as each one has a 50% risk of passing the mutated allele to their offspring. As the mutated allele in each patient would be passed from an affected mother, any affected offspring would be at risk for PHP1a and hormone resistance rather than POH [5].

The long-term prognosis of patients with POH is uncertain because only a few patients have been followed beyond adolescence. In these few patients, the disease has followed a slower progression during adulthood [2,5]. In patient-1, the disease was limited to the left arm with severe growth retardation and contractures of the thumb, wrist and elbow as a result of deep heterotopic ossification. In patient-2 the lesions were more dispersed and remained superficial into adulthood, thus excluding POH. In both patients, the disease had stabilized.

Presently, there is no treatment or prevention for *GNAS*-associated disorders of cutaneous heterotopic ossification although anecdotal reports of therapies have appeared in the literature [2,8]. Surgical resection of the lesions can be followed with recurrences or complications, especially when the ossification is progressive and deep [2,5,6,7]. Bisphosphonate treatment has been successful in children with osteoporosis, various skeletal dysplasias and heterotopic ossification [10,11,12]. Some researchers investigated the result of bisphosphonate therapy in patients with heterotopic ossification. In 2006 a girl with progressive osseous heteroplasia received treatment with bisphosphonate, which correlated with diminishing of the progression of new ectopic bone formation [8]. More research is needed to investigate if this treatment is successful in more patients and to investigate the long-term results. Early diagnosis is important so that optimal care and genetic counselling can be provided and unnecessary treatments can be avoided.

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Figure 1. Photograph and radiograph of patient-1

A) Photograph of the left upper limb of patient-1 at 2.5 years of age. The skin is reddish-purple in colour with a linear papular pattern of cutaneous heterotopic ossification. The thumbs appear deformed and rigid.

B) Radiograph of the left upper limb of patient-1 at eight years of age. Note the characteristic web-like reticular pattern of POH-type heterotopic ossification most prominent on the radial side of the forearm with ankylosis of the elbow and involvement of the thumb and radius.

Figure 2. Photographs and radiographs of patient-2 at 18 years of age

- A) Photograph of the left hand. The short thumb and the short fourth and fifth metacarpals are well seen on the photograph.
- B) Photograph of the right foot. A small area of osteoma cutis and subcutaneous heterotopic ossification is seen on the dorsum of the foot. Also visible is the short fourth toe.
- C) Radiograph of the right hand. (A) the superficial ectopic mineralization vs. the sesamoid bone of first metacarpal; (B) the shortened 4th+5th metacarpals; and (C) the Madelung deformity
- D) Radiograph of the left foot. Note the short fourth metatarsal and the superficial heterotopic ossification on the lateral side of the fifth metatarsal.

A. Case 1

B. Case 2

Figure 3. Deletions in the *GNAS* gene in two patients with *GNAS*-associated disorders of cutaneous ossification

The *GNAS* genes of controls and patients were examined by DNA sequence analysis of genomic DNA. Electropherograms of regions that include the identified mutations in (A) Case 1 and (B) Case 2 are shown. Lower portions of each panel show the DNA sequences and corresponding amino acid sequences for the relevant regions of the *GNAS* gene for each patient. For Case 1, the DNA sequence begins at cDNA position c.1093 in codon 365; the deleted nucleotides in the mutant allele at cDNA position c.1107–1108 are indicated by grey shading in the normal allele sequence. In Case-2, the DNA sequence begins at cDNA position c.340 in codon 114; the deleted nucleotide in the mutant allele at cDNA position c.355 is indicated by grey shading in the normal allele sequence. Both deletions cause a codon reading frame-shift leading to a premature stop codon.

Table 1

Features of heterotopic ossification in POH, FOP, and AHO/PHP1a

<i>Feature</i>	<i>POH</i>	<i>FOP</i>	<i>AHO</i>	References
Genetic transmission	Autosomal dominant	Autosomal dominant	Autosomal dominant	[1,4,13]
Congenital malformation of great toes	–	+	–	[1,4,13]
Congenital papular rash	+	–	–	[1]
Cutaneous ossification	+	–	+/-	[1,4]
Subcutaneous ossification	+	–	+/-	[1,4]
Muscle ossification	+	+	–	[1,13]
Superficial to deep progression of ossification	+	–	–	[1]
Severe limitation of mobility	+	+	–	[1,13]
Severe flare-ups of disease	–	+	–	[13]
Ectopic ossification after intramuscular injections	–	+	–	[13]
Ectopic ossification after trauma	+/-	+	–	[1,13]
Regional patterns of progression	–	+	–	[13]
Definitive treatment available	–	–	–	[8,4,13]
Predominant mechanism of ossification	Intramembranous	Endochondral	Intramembranous	[1,4,13]
Inflammatory perivascular and muscle infiltrate	–	+	–	[13]
Hematopoietic marrow in ectopic bone	+/-	+	–	[1,13]
PTH resistance	–	–	+ *	[4]
Hypocalcemia and hyperphosphatemia	–	–	+	[1,4,13]
Genetic mutations	Heterozygous inactivating mutations of (paternal allele) <i>GNAS</i> , the gene encoding the α -subunit of G-stimulatory protein adenylyl cyclase	Activating mutation of the gene encoding the BMP type 1 receptor <i>ACVR1/ALK2</i>	Heterozygous inactivating mutations of <i>GNAS</i> ,* the gene encoding the α -subunit of G-stimulatory protein adenylyl cyclase	[5,413]

* PHP1a is the clinical diagnosis for the presence of AHO features and hormone resistance. PHP1a is associated with mutations in the maternal allele of *GNAS*.