Mild progressive osseous heteroplasia overlap syndrome with PTH and TSH resistance appearing during adolescence and not early childhood

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Abstract

Purpose Progressive osseous heteroplasia (POH), a genetic disorder, is associated with Albright’s hereditary osteodystrophy (AHO), pseudohypoparathyroidism, and primary osteoma cutis and has common features of superficial ossification and GNAS-inactivating mutations. Disorders due to GNAS-inactivating mutations are classified as “inactivating parathyroid hormone (PTH)/PTHrP signaling disorder type 2.” This study reports a case of mild POH overlap syndrome to improve understanding of genotype–phenotype correlations.

Methods A 13-year and 6-month-old Japanese boy was referred to our hospital with a chief complaint of the lower limb length difference. He underwent clinical, biochemical, radiological, and genetic studies.

Results He showed sporadic GNAS mutation, deep ectopic ossification, small for gestational age (SGA), congenital tooth defect, and lack of AHO features; he met the diagnostic criteria for POH, and mild PTH and TSH resistance was detected. He had constant hyperphosphatasemia and hypocalciuria. At the age of 10 years, he occasionally experienced high iPTH levels. The pituitary stimulation test showed a normal response of all hormones at 3 years of age, but TSH response was decreased (previously 0.770, peak value 4.144 μIU/mL) in the TRH loading test at age 13 years and 6 months. DNA analysis showed a heterozygous p.D189MfsTer14 mutation of GNAS. The parents did not carry this mutation.

Conclusion We report a rare case of POH overlap syndrome with PTH/TSH resistance that appeared in adolescence rather than early childhood. Cases diagnosed with POH in early childhood also require reassessment during adolescence. Further studies of the GNAS heterozygous mutation p.D189MfsTer14 may reveal factors involved in POH overlap syndrome.

Keywords POH overlap syndrome · Deep ectopic ossification · Sporadic GNAS mutation · PTH/TSH resistance

Introduction

Progressive osseous heteroplasia (POH) is an extremely rare hereditary disease characterized by progressive ectopic ossification [1]. POH is a genetic disorder associated with Albright’s hereditary osteodystrophy (AHO), pseudohypoparathyroidism (PHP), and primary osteoma cutis and has common features of superficial ossification and GNAS-inactivating mutations. Patients with POH usually do not have parathyroid hormone (PTH) resistance; however, there have been reports of POH overlap syndrome where AHO or PHP features are present besides POH features [2]. Diagnosis of POH overlap syndrome is made on the basis of only clinical symptoms. There are currently only a few detailed reports of POH overlap syndrome, and thus, the condition is poorly understood. We report a rare case of
POH overlap syndrome with PTH/TSH resistance that appeared in adolescence but not during early childhood.

Materials and methods

Subject

A 13-year and 6-month-old Japanese boy was referred to our hospital with a chief complaint of the lower limb length difference. He was born at 32 weeks and 4 days gestation and was SGA (weight of 928 g and height of 36.0 cm). His medical history revealed a congenital tooth defect. His two upper teeth and four lower teeth were congenitally missing. He has been receiving growth hormone therapy for SGA short stature since the age of 3 years and 2 months.

When he entered junior high school, he noticed a right > left difference in leg length (Fig. 1a). An abnormal shadow was discovered on the foot during the presurgical inspection of orthopedic surgery for lower limb length difference, which was suspected to be progressive ossifying fibrodysplasia. He was referred to the Departments of Clinical Genetics and Metabolic Endocrinology.

Biochemical and imaging analyses

Blood and urine tests were conducted regularly from age 7 years and 2 months to 13 years and 2 months at his original hospital. He underwent biochemical and radiological studies, including ultrasonography, of the abdomen. From the day before the insulin tolerance test, GH administration was discontinued and the insulin tolerance test was performed.

Genetic analyses

We conducted genetic analysis after obtaining written informed consent from the patient and parents. All procedures were reviewed and approved by the institutional review board of Kobe University School of Medicine and were conducted according to the ethical standards of the 1964 Declaration of Helsinki. Genomic DNA was extracted from peripheral blood mononuclear cells using the QuickGene whole blood kit (Kurabo, Osaka, Japan). We utilized an Illumina® TruSight™ One sequencing panel on a MiSeq platform following the manufacturer’s instructions (Illumina San Diego, CA, USA). Mutations were confirmed via standard Sanger sequencing.

Results

Subject

The patient was 157.3-cm tall (−0.27 SD) and weighed 43.4 kg (−0.66 SD). The average height and weight of similarly aged Japanese boys (2000) are 160.0 ± 7.7 cm and He has never been overweight. c–f X-ray of bones. c No brachydactyly on either foot. d Shortening of the left femoral neck. e–f Ectopic ossification of the right hand and left foot
50.4 ± 10.5 kg, respectively. He has never been overweight (Fig. 1b). Signs of puberty were Tanner stage 3 for testicles (8 mL as measured using a Prader orchidometer) and Tanner stage 3 for pubic hair. He had no signs of AHO, such as round face, obesity, brachydactyly, metacarpal/metatarsal shortening, or developmental delay (Fig. 1c). No subcutaneous osteoma was found on his skin. Ectopic ossification appeared on the outside of his right hand at age 5 years and on the sole of his left foot at age 9 years.

**Biochemical and imaging analyses**

The patient had persistent hyperphosphatasemia (4.7–6.4 mg/dL [normal, 2.4–4.3 mg/dL]) and hypocalciuria. Assessment of hypocalciuria showed a serum calcium level of 9.6 mg/dL and FE Ca was low (0.00%; mean FE Ca in the presence of normocalcemia was 2% [range: 1.5–3.0%]). At the age of 10 years, he occasionally had high iPTH levels. Occasionally, high iPTH was observed on four evaluations, with a level of 67–87 pg/mL (normal range, 10–65 pg/mL). Alkaline phosphatase and 25-hydroxyvitamin D levels were normal. In addition, thyroid hormone, free T3 (3.57 pg/mL [normal range: 2.13–4.07 pg/mL]), free T4 (1.29 ng/dL [normal range: 0.95–1.74 ng/dL]), and TSH (3.415 μIU/mL [normal range: 0.5–4.2 μIU/mL]) levels were normal. His renal function was impaired (CKD stage 2). He had no albuminuria or proteinuria, and his estimated glomerular filtration rate was 61.1–80.1 mL/min/1.73 m². Imaging findings revealed his right kidney measured 10.2 × 5.1 cm with multiple renal calcifications.

The urinary cyclic adenosine monophosphate (cAMP) response to 100-mg PTH administered intravenously was normal: 510 pmol/mL before administration and 42,000 pmol/mL 1 h after administration (normal, cAMP levels increase at a rate of ten times or more).

The pituitary stimulation test showed that all hormones responded normally at 3 years of age, but the TSH response decreased (previously 0.770, peak value 4.144 μIU/mL) in the TRH loading test at 13 years and 6 months of age. Concurrent PRL reactions were normal, which demonstrated that TRH loading was not an issue. GH, LH, and FSH responded normally.

**Genetic analyses**

DNA analysis showed a heterozygous p.D189MfsTer14 mutation of the GNAS gene. The parents did not carry this mutation (Fig. 3).
Table 1 Clinical and molecular characteristics of cases of mild POH overlap syndrome reported in the literature

| Reference | GNAS mutation | Familial transmission/ mutated allele | Age of onset of heterotopic ossification | Age of onset of PTH resistance | Age of onset of TSH resistance |
|-----------|----------------|---------------------------------------|-----------------------------------------|-------------------------------|-------------------------------|
| Lebrun, M., et al. [10] | c85C> T | De novo/maternal | 6 months | 3 years | 3 years |
| Elli, F.M., et al. [11] | c.565_568delGACT | De novo/maternal | 6 months | 1 year | 1 year |
| Gelfand et al. [12] | c.546delC | De novo/unknown | 1 month | 16 months | 4 months |

Discussion

We present a case of POH overlap syndrome (POH/PHP1a/1c) who showed a sporadic GNAS mutation, deep ectopic ossification, SGA, congenital tooth defect, and lack of AHO features. This patient met the diagnostic criteria for POH, and mild PTH and TSH resistance was detected, as shown in Fig. 2 (TRH-serum TSH). The normal range of TRH stimulation is 5–30 μIU/mL. The peak value was observed after 15–30 min. The TRH stimulation values observed when the patient was 3 years old were normal, but those observed at 14 years of age decreased significantly, and the peak value was below the normal level, as indicated by a black broken line, indicating a low reaction of TSH to TRH stimulation.

Because GNAS genes concern the signaling of various hormones, various hormonal tolerances appear when GNAS genes are in an abnormal state. TSH tolerance is one such example, and TSH reactions to TRH stimulation decrease when TSH tolerance appears. Although the patient did not exhibit PHP, mild TSH tolerance was diagnosed because of a low reaction of TSH to TRH stimulation.

PHP, the first known post-receptor hormone resistance, is caused by a partial deficiency of the α subunit of the stimulatory G protein (Gsα), which is a key component of the PTH/PTHrP signaling pathway. Since its first description, besides the molecular basis of PHP, various studies have revealed the existence of numerous subtypes and differential diagnoses associated with genetic alterations of the PTH/PTHrP pathway. The clinical and molecular overlap of PHP subtypes and other related disorders presents challenges for both differential diagnosis and genetic counseling [3].

In 2016, the EuroPHP network developed a new classification that encompasses all disorders involving impairments in PTH and/or PTHrP CAMP-mediated pathways [4]. Elli and Mantovani reviewed the major and minor features characterizing inactivating PHP or PTH/PTHrP signaling disorders (iPPSDs) as a group and the specificities and overlap associated with the most frequent subtypes [3]. Their descriptions on POH are in line with our findings.

Because there are only a few detailed reports of POH overlap syndrome, there remain numerous unclear points regarding additional AHO or PHP features that are present alongside POH features. The diagnosis of POH overlap syndrome is made on the basis of only clinical symptoms [2]. There are further uncertainties about POH. For example, our patient was first diagnosed at age 13 years and 6 months despite POH usually being diagnosed within the first year of life [5]. Moreover, although Shore et al. demonstrated that most cases of POH are caused by paternally inherited inactivating mutations of GNAS [6], our patient showed both POH and PHP Ia, which are apparently due to a de novo mutations of GNAS.

Recently, Pereda et al. proposed new criteria and classifications of iPPSDs. Moreover, current work is focused on improving classifications of PHP and related disorders [7]. POH is diagnosed on the basis of three major criteria: superficial heterotopic ossification (HO) that progresses to deep connective tissue, no more than two AHO features, and no PTH resistance [8]. Progressive extension of HO into deep connective tissue, congenital tooth defects, and shortening of the left femoral neck are considered AHO symptoms. However, PTH tolerance is a characteristic symptom of PHP1A [1]. As shown in Table 1, hormone resistance was not observed at the time of initial POH identification, and hormone tolerance appeared months to years later in this patient with mild POH overlap syndrome. In this case, PTH tolerance was diagnosed because the patient had mild POH and was aged >13 years. Therefore, this case is mild POH overlap syndrome (POH/PHP1).

It has been recently reported that severe POH without PHP1A/1C features is caused by paternally inherited inactivating mutations of GNAS, whereas mild cases of POH with AHO/PHP1A features are caused by maternal inherited inactivating mutations of GNAS [9].

The heterozygous mutation p.D189MfsTer14 of GNAS identified in our case is not only a POH hereditary mutation but also a mutation hotspot of AHO/PHP1A, so it may exhibit a wide range of phenotypes [8, 10]. Genetic background, modified genes, epigenetic modifications, and environmental factors are believed to be factors that contribute to POH
overlap syndrome [9]. Further studies of the GNAS heterozygous mutation p.D189MfsTer14 may reveal the factors that are involved in POH overlap syndrome.

It remains unclear whether POH overlap syndrome is associated with progressive bone age, the appearance of intellectual impairment, or gonadal dysfunction [1]. In our case, there were no abnormalities in bone age progression, intelligence, or gonadal function. Given the rarity of POH/PHP1C/1C, further cases will need to be investigated to elucidate these uncertainties.

In summary, we present a rare case of POH overlap syndrome (POH/PHP1A/1C), which was diagnosed only by clinical symptoms. POH is usually diagnosed by the age of 1 year; however, our patient was first diagnosed at age 13 years and 6 months because the bone lesions were much milder than previously reported. Genetic background, modified genes, epigenetic modifications, and environmental factors are believed to be the factors that contribute to POH overlap syndrome [9]. Further studies of POH cases will enable the identification of factors associated with POH overlap syndrome. Moreover, additional studies of the GNAS heterozygous mutation p.D189MfsTer14 will provide a better understanding of the factors involved in POH overlap syndrome.

Author contributions Conceptualization and writing—original draft preparation: K.O.; formal analysis: N.M. and K.I.; investigation: G.N., A.M., and M.N.; resources: A.N.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Consent for publication Written informed consent was obtained from the patient and his parents for publication of this case report and any accompanying images.

Ethics approval All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee (Hyogo Prefectural Kobe Children’s Hospital committee + reference number: R3-1) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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