Patient report

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Pseudohypoparathyroidism type Ia: a novel *GNAS* mutation in a Brazilian boy presenting with an early primary hypothyroidism

Abstract: Pseudohypoparathyroidism type Ia (PHP Ia) is a rare disease characterized by an elevated parathyroid hormone due to the resistance to its action in target tissues. We report a new *GNAS* mutation causing PHP Ia and an atypical early-onset primary hypothyroidism. A 3-year-old boy was diagnosed with obesity, delayed pyschomotor development, and round face. The laboratory evaluation at the age of 1 year showed primary hypothyroidism, hypocalcemia, hyperphosphatemia, elevated alkaline phosphatase, and parathyroid hormone. These data led to the diagnosis of PHP Ia. Molecular analysis revealed a novel missense mutation in *GNAS* exon 1 (TCG→CGC, Cys3→Arg) in both the child and his mother. Although previously reported cases described delayed subclinical hypothyroidism as the more common thyroid abnormality, we report a not previously described *GNAS* mutation associated with an atypical early-onset primary hypothyroidism. These observations broaden the clinical spectrum of PHP Ia and its associated mutations.

Keywords: hypocalcemia; hypothyroidism; pseudohypoparathyroidism.

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Introduction

Pseudohypoparathyroidism (PHP) is a rare familial (inherited) or sporadic disorder that refers to a heterogeneous group of diseases characterized by clinical and laboratory findings of hypoparathyroidism (hypocalcemia and hyperphosphatemia), although with elevated plasma levels of parathyroid hormone (PTH) due to the resistance to PTH action in target tissues (1, 2).

The pattern of hormonal resistance in PHP is caused by the inactivating mutations of the *GNAS* gene, which encodes the stimulatory G-protein α-subunit (Gsα), a signaling protein whose activity is essential for the actions of PTH, thyrotropin (TSH), gonadotropins, and human growth hormone releasing factor (GHRH) (1, 2). The *GNAS* gene is located on the long arm of chromosome 20 in the region 13.1–13.2 and contains 13 exons. The inactivating mutations have been detected in all exons, with 20% of the mutations occurring in exon 7 (2, 3).

Transmission is autosomal dominant with variable disease expression and is caused by mutations in the maternal allele (haploinsufficiency with paternal imprinting). The presence of mutations in the paternal allele, in turn, leads to a condition known as pseudopseudohypoparathyroidism (PPHP), which is characterized by Albright hereditary osteodystrophy (AHO) in the absence of hormone resistance (4).

This case report describes a patient with clinical diagnosis of PHP Ia, whose molecular analysis showed a new and not previously described missense mutation in exon 1 (TCG→CGC, Cys3→Arg) associated with an unusual early-onset primary hypothyroidism.

Case report

A 3-year-old boy was diagnosed with obesity, round face, and delayed neuropsychomotor development since the age of 7 months. He was born at term, with a birth weight of 3500 g and a birth length of 49 cm. The physical examination revealed weight of 18.4 kg (p>95th), height of 93 cm (p=50–75th), body mass index of 21.27 kg/m^2 (p>95th),

Table 1 Laboratory investigation during the initial evaluation at the age of 1 year.

Laboratory evaluation	Results
Calcium, normal: 2.1–2.6 mmol/L (8.5–10.5 mg/dL)	1.6 mmol/L (6.4 mg/dL)
Phosphorus, normal: 1.16–2.1 mmol/L (3.6–6.5 mg/dL)	2.6 mmol/L (7.9 mg/dL)
Alkaline phosphatase, normal: <645 U/L	545 U/L
25(OH) vitamin D, deficiency: ≤37.4 nmol/L (≤15 ng/mL)	37.1 nmol/L (14.3 ng/mL)
1,25(OH) vitamin D, normal: 43.2–187 pmol/L (18–78 pg/mL)	194 pmol/L (81 pg/mL)
PTH, normal: 15–65 ng/L (15–65 pg/mL)	515 ng/L (515 pg/mL)
Free T4, normal: 14.1–29.7 pmol/L (1.1–2.0 ng/dL)	11.8 pmol/L (0.8 ng/dL)
TSH, normal: 1.36–8.8 mU/L	30 mU/L
IGF-I, normal: 6.68–39.6 nmol/L (51–303 ng/mL)	3.37 nmol/L (25.8 ng/mL)
IGFBP-3, 0.8–4.3 mg/L	1.7 mg/L
Clonidine stimulation test for measurement of growth hormone, peak value: >7 μg/L (>7 ng/mL)	0 min: 4.3 μg/L (4.3 ng/mL), 60 min: 1.6 μg/L (1.6 ng/mL), 90 min: 1.5 μg/L (1.5 ng/mL)

IGF, insulin-like growth factor; IGFBP-3, insulin-like growth factor binding protein-3.

head circumference of 52.2 cm (p=75–90th), waist circumference of 61 cm (p>90th), round face, and delayed neuropsychomotor development.

The laboratory investigation at the age of 1 year is summarized in Table 1. Thyroid ultrasound was normal. Radiologic assessment did not show brachydactyly or subcutaneous calcifications. Laboratory testing of the patient's mother ruled out PHP, although she had dysmorphism suggestive of PPHP, such as short stature (1.48 m) and brachydactyly of the first and third fingers of both hands.

Genomic DNA was extracted from the patient's peripheral blood cells and direct sequencing of *GNAS* Gsα-coding exons 1–13 was performed as previously reported (5), revealing a missense mutation in exon 1 (TGC→CGC, Cys3→Arg) (Figure 1). This mutation, not previously reported in the literature, affects a residue that when mutated is probably responsible to alter the membrane-binding domain of the Gsα protein, and it is thus likely to be the cause of the clinical manifestations of PHP Ia in the patient. Molecular analysis revealed a similar genetic mutation in the patient's mother, who was diagnosed as having PPHP.

During the last evaluation, at the age of 3.6 years, the patient was receiving levothyroxine, calcium and vitamin D replacement, and growth hormone replacement was scheduled. The patient is presently clinically stable, obese, with slowly progressive neurologic development, normocalcemia and phosphatemia, and adequate thyroid hormone levels.

Discussion

The most common type of PHP is PHP Ia. The resistance to PTH is caused by Gsα deficiency due to the inactivating mutations of the gene (4). Besides the resistance to PTH, patients may have the resistance to TSH, calcitonin, GHRH, and gonadotropins.

PHP Ia is also associated to AHO that classically manifests itself with short stature, round face, small nose, flat nasal bridge, brachymetacarpia, brachydactyly (mainly of the fourth and fifth fingers), ossification of soft tissues,

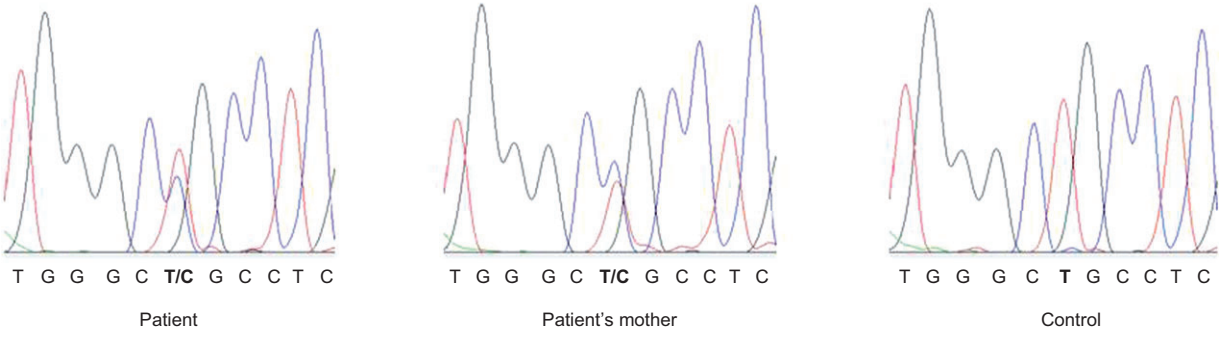

Figure 1 Direct sequencing of the patient's amplified genomic DNA fragments revealing a heterozygous missense mutation in exon 1 involving the third amino acid of the Gsα protein (T54C, Cys3Arg).

centripetal obesity, and, in some cases, mental retardation (1). Although a short stature is a typical manifestation of AHO, normal or above average stature usually occurs in early childhood probably related to underlying obesity (6). Intracranial calcifications may manifest themselves by late-onset epileptic seizures and extrapyramidal features (7). Subcutaneous ossifications in the neonatal period may represent an early manifestation of PHP Ia or Ic (8, 9). The phenotype is variable, becoming more evident in the fourth year of life. The patient in this study had centripetal obesity, round face, and delayed neuropsychomotor development.

PHP is characterized by hypocalcemia, hyperphosphatemia, and elevated levels of PTH in individuals with normal renal function (2). The resistance to PTH usually develops early in life and before hypocalcemia (10). Hypocalcemia usually manifests itself after the age of 5 years (10) or becomes evident only after the prepubertal growth spurt when calcium requirements are greater (1).

Hypothyroidism is frequent in PHP Ia. The resistance to TSH is usually mild and the levels of thyroid hormones are normal or slightly reduced (10). This disorder tends to appear at a later moment, with early-onset and congenital hypothyroidism being a rare event (11, 12). This patient, on the contrary, had an early diagnosis of primary hypothyroidism, at the age of 1 year. Because he did not undergo neonatal thyroid screening, we cannot assess if he was born with such a disorder.

Hypogonadism, more common in females, manifests itself by mild hypoestrogenism, which is caused by the partial resistance to gonadotropins (10). Growth hormone deficiency suggests the resistance to GHRH and contributes to obesity and short stature (13).

The patient in this study had hypocalcemia, hyperphosphatemia, elevated PTH, hypothyroidism, and growth hormone deficiency. He also had a mild vitamin D deficiency, which did not explain the hypocalcemia, hyperphosphatemia, and elevated PTH levels, because the PTH persisted elevated even after the correction of the vitamin D deficiency (14).

The missense mutation presented by this patient in exon 1 (TGC→CGC, Cys3→Arg) was not previously reported in the literature and may be responsible for the atypical phenotype of early-onset primary hypothyroidism, confirming the need for further studies and genetic counseling. Our observations broaden the clinical spectrum of PHP Ia. A further investigation of patients with similar mutation is warranted.

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Conflict of interest statement

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