Pseudohypoparathyroidism vs. tricho-rhino-phalangeal syndrome: patient reclassification

Abstract

Objectives: Given that tricho-rhino-phalangeal syndrome (TRPS) and pseudohypoparathyroidism/pseudopseudohypoparathyroidism (PHP/PPHP) are very rare monogenic disorders that share some features (distinctive facies, short stature, brachydactyly and, in some patients, intellectual disability) that lead to their misdiagnosis in some cases, our objective was to identify clinical, biochemical or radiological signs that could help to distinguish these two syndromes.

Methods and results: We report on two cases, which were referred to the Endocrinology and Pediatric Endocrinology Services for obesity. Clinical evaluation initially suggested the diagnosis of PHP-Ia [phenotype suggestive of Albright hereditary osteodystrophy (AHO) with parathyroid hormone (PTH) resistance] and PPHP (phenotype resembling AHO, without PTH resistance), but (epi)genetic analysis of the GNAS locus ruled out the suspected diagnosis. Further clinical re-evaluation prompted us to suspect TRPS, and this was confirmed genetically.

Conclusion: TRPS was mistakenly identified as PHP/PPHP because of the coexistence of obesity and brachydactyly, with PTH resistance in one of the cases. Specific traits such as sparse scalp hair and a pear-shaped nose, present in both cases, can be considered pathognomonic signs of TRPS, which could help us to reach a correct diagnosis.

Keywords: bulbous nose; pseudohypoparathyroidism; pseudopseudohypoparathyroidism; sparse hair; tricho-rhino-phalangeal syndrome.

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Introduction

Tricho-rhino-phalangeal syndrome (TRPS-I, OMIM #190350; TRPS-III, OMIM #190351) and pseudohypoparathyroidism/pseudopseudohypoparathyroidism (PHP-Ia, OMIM #103580; PPHP, OMIM #612463) can be clinically confused with each other because they have an overlapping phenotype with rare or subtle dysmorphic features, short stature, brachydactyly and intellectual disability (1–4). Typical facial dysmorphic traits described in TRPS [sparse, slowly growing scalp hair; laterally sparse eyebrows; a bulbous tip of the nose (pear-shaped nose); and long flat philtrum] (2) can be very mild, thus complicating the clinical diagnosis. We report on a family and an isolated case initially diagnosed as PHP-Ia/PPHP, which we later identified as a mutation in the TRPS1 gene, highlighting both the features that can be shared by the two syndromes and those that finally helped us to reach the correct diagnosis and confirm it with the appropriate genetic study.

Subjects and methods

Subjects

Patient 1

The proband, a 31-year-old woman, was referred to the Endocrinology Department for morbid obesity. She had a personal history of obesity from her first pregnancy at the age of 18, with a progressive increase in weight. She did not have any other clinical complications but occasionally took pain relief medication. The patient had menarche at age 12, and her menstrual cycles were irregular with
oligomenorrhea, without presenting amenorrhea. She had had four uncomplicated pregnancies, which resulted in normal deliveries, and none of her children had fetal macrosomia. The proband's mother and brother, who were short in stature, were both affected by polyarthrosis. The patient did not show any symptoms suggestive of hormonal dysfunction. She tended to have a high-calorie diet, and her ability to exercise was limited by arthralgias of both hips and knees. She had learning difficulties during childhood. Her height was 141.5 cm (–4 SD) and body mass index (BMI) was 42.7 kg/m². On physical examination, she was observed to have facial features including a round face, sparse hair, a thin upper lip and a prominent lower lip, a pear-shaped nose, tooth hypoplasia, and stubby fingers and toes (Figure 1A–C). Her round face, brachydactyly, shortening of the III–V metacarpals and middle phalange, together with her very short stature, suggested an Albright hereditary osteodystrophy (AHO) phenotype. A bone X-ray survey and thorough biochemical and hormonal tests were performed. Her karyotype was normal (46, XX). However, repeated blood tests showed normal levels of calcium and phosphorus with parathyroid hormone (PTH) levels above the normal limit (70–110 pg/mL; reference range 10–40 pg/mL) and normal 25-OH-vitamin D levels (72.8 ng/mL). Urine calcium level was also normal (100–130 mg/24 h) in repeated measurements. Basal pituitary function was normal except for low insulin-like growth factor 1 (IGF-1) levels, which were below the age-adjusted normal level (53 ng/mL), which were confirmed in several measurements. The possibility of isolated growth hormone (GH) deficiency was further examined and confirmed by the results of two GH provocation tests: a glucagon test (GH peak <0.7 ng/mL) and an insulin hypoglycemia test (GH peak of 0.1 ng/mL with hypoglycemia of 40 mg/dL). Hand X-rays revealed cone-shaped epiphyses of all middle and I–IV proximal phalanges of both hands and a shortening of the metacarpals: IV and V of the right hand and III and V of the left one (Figure 2A). A lumbar spine X-ray revealed sacralization of the L5 vertebra and bilateral last-rib hypoplasia. Knee X-rays showed marked hypoplasia of the medial tibial condyles and unilateral hypertrophy of the internal femoral condyle.

Two of her children had a normal stature, normal X-ray surveys and no dysmorphic traits (Figure 2B and C). However, her 13-year-old daughter had a height in the 10th percentile, brachydactyly, clinodactyly and mild dysmorphic traits (wide mouth, sparse hair, long philtrum and bulbous tip of the nose), but had no learning difficulties. Similar to those of her mother, results of her hand X-rays showed cone-shaped epiphyses of all middle and I–IV proximal phalanges of both hands and a shortening of the metacarpals: III–V of the right hand, and III and V of the left hand (Figure 2C). No alterations were identified in the calciotropic axis (calcium, phosphorus and PTH), and the IGF-1 level was normal.

The proband’s mother and brother had a similar phenotype, but further medical evaluations and photographs were not available.

Figure 1  Phenotypic appearance of patient 1 (A) and patient 2 (D), revealing a round face, sparse hair, thin lips and pear-shaped nose. (B and E) Hands and (C and F) feet with stubby fingers and toes, and brachydactyly.
An 11-year-old girl was referred to the pediatric endocrinologist because of overweight and a family history of obesity and type 2 diabetes. She was born at term by normal delivery with a weight of 2600 g (p6) and a length of 49 cm (p39). She had a normal psychomotor development, although she has been attending speech therapy since 5 years of age. The onset of pubertal signs started at 8½ years of age. Anthropometric measurements included the following: height of 139.8 cm (p18) and a weight of 50.2 kg (p79), yielding a BMI of 25.6 kg/m² (+1.96 SD). She had sparse hair, laterally sparse eyebrows, long flat philtrum, thin upper vermillion border, a pear-shaped nose, protruding ears (Figure 1D), shortened fingers (Figure 1E) and toes, and flat feet (Figure 1F). Her karyotype was normal (46,XX). Thorough biochemical and hormonal analyses (blood count; hepatic, renal and lipid profiles; serum levels of calcium, phosphorus, PTH, IGF-1, thyroid-stimulating hormone, follicle-stimulating hormone and luteinizing hormone) found completely normal results.

Interestingly, hand X-rays showed cone-shaped epiphyses of the middle and proximal II–IV phalanges and I proximal phalanx and a shortening of the II–V metacarpals (Figure 2D), initially suggesting a diagnosis of PPHP.

**Patient 2**

Genetic analyses were performed after obtaining the informed consent of the patient and/or parents (in the case of minors). Genomic DNA was extracted from peripheral blood mononuclear cells using a QIAamp DNA mini kit (QIAGEN, Düren, Germany). Firstly, the GNAS locus was analyzed, including sequencing of the GNAS 13 coding exons and evaluation of the methylation, as previously described (5). No abnormalities were identified (data not shown). Then intronic and, when required, exonic primers were used to amplify the coding exons and intron-exon junctions of TRPS1 (ENST00000395715) (primers available on request). Polymerase chain reaction products were analyzed by direct nucleotide sequence analysis using standard methods on an ABI 3500 genetic analyzer (Applied Biosystems, Foster City, CA, USA).

**Results**

Patient 1 and her daughter were clinically diagnosed with PHP-Ia because of the recurrent PTH resistance (only in the index) and phenotype characteristics of AHO. The molecular study did not reveal genetic or epigenetic alterations in the GNAS locus. After a clinical re-evaluation, mild dysmorphic traits including sparse hair and bulbous nose tip suggested TRPS. Direct sequencing of the TRPS1 gene revealed an adenine deletion (c.2830delA) in exon 7, which leads to a frameshift mutation (p.Arg944Glyfs*3) (Figure 3A). This mutation has not been previously reported, but the cosegregation within the family, the in silico studies and the absence of mutation in 100 healthy controls suggest the pathogenicity of the mutation.

![Figure 2](image) Hand X-rays of (A) patient 1 showing cone-shaped epiphyses and outcarving cones of the middle and terminal phalanges of both hands, a shortening of the metacarpals and proximal and middle phalanges; (B) the unaffected son and (C) the affected daughter. (D) Left-hand X-ray of patient 2 also revealing cone-shaped epiphyses and outcarving cones of the middle and terminal phalanges, and a shortening of the metacarpals and proximal and middle phalanges.
In contrast, patient 2 was initially given the diagnosis of possible PPHP owing to the combination of language delay, obesity, short stature and brachydactyly without PTH resistance. After obtaining negative (epi)genetic results at the GNAS locus, TRPS1 analysis identified a de novo mutation in exon 6, p.Arg921Gln (Figure 3B), which is considered a recurrent mutation [previously reported as p.Arg908Gln (2, 6)].
Discussion

Albright hereditary osteodystrophy (AHO), described more than 70 years ago by Albright et al. (7), is a clinical entity that encompasses heterogeneous clinical findings including obesity, short stature, variable degrees of mental retardation, brachymetacarpia and brachymetatarsia, as well as subcutaneous calcifications. It is one of the few monogenic hereditary obesity and mental retardation syndromes. Its prevalence is estimated to be approximately 0.79/100,000 (according to the Orphanet Report Series, November 2008).

This syndrome is often associated with pseudohypoparathyroidism (PHP-Ia, OMIM #103580) (7), a state of endocrine resistance to peptide hormones eliciting their signaling through the Gsα pathway. The current classification distinguishes between several entities of PHP with and without AHO, and AHO without endocrine abnormalities [pseudopseudohypoparathyroidism (PPHP, OMIM #612463)] (1), all of which are mainly caused by (epi) genetic alterations within or upstream of the GNAS locus. However, in a large subset of patients, it is not possible to make a definitive diagnosis with a conclusive correlation between clinical, biochemical and molecular genetic findings. In fact, the AHO phenotype is not specific to PHP or PPHP, as it is also present in other syndromes such as the brachydactyly mental retardation syndrome (or AHO-like syndrome, OMIM #600430) and can even be misdiagnosed as other entities such as acrodysostosis (ACRDYS1, OMIM #101800; ACRDYS2, OMIM #614613) (8–10).

TRPS is a rare syndrome, the phenotype of which could also be easily confused with the AHO phenotype given the presence of brachydactyly and short stature. Even though obesity is among the AHO signs, but not those of TRPS, the patients reported in this article were referred to the endocrinologist for obesity (or overweight with a family history of obesity associated with type 2 diabetes). It is possible that obesity or overweight in the patients reported in the present work might have acted as a confusing factor, as they are attributable to the current obesity pandemic. Other clinical characteristics suggestive of an AHO phenotype such as a round face, shortening of the metacarpals and short stature were also present. Besides, hormonal analysis of patient 1 revealed elevated serum PTH levels with normal phosphorus and calcium values. This normocalcemic hyperparathyroidism was not secondary to a 25-OH-vitamin D deficiency/insufficiency, and it was deduced that there was resistance to PTH. Though uncommon, these biochemical characteristics have already been described in PHP-Ia patients with GNAS loss-of-function mutations (5, 11, 12). In contrast, isolated GH deficiency was also observed in this patient and resistance to growth hormone-releasing hormone has been described in PHP-Ia patients (13). However (epi)genetic analysis of the GNAS locus obtained normal results, which have been described in nearly 30% of suspected cases of PHP/PPHP (14). Clinical re-evaluation of our patients revealed some mild but specific features that prompted us to suspect the possibility of TRPS such as a pear-shaped nose, sparse hair and tooth hypoplasia. The genetic study of TRPS1 revealed patient 1 and her affected daughter carried a previously undescribed nonsense mutation (c.2830delA) that cosegregates within the family with the phenotype. Patient 2 presents a previously described recurrent de novo mutation (Arg921Gln) (2, 6). Based on our findings, we propose exhaustive clinical re-evaluation of each PHP/PPHP patient without (epi) genetic alterations at the GNAS locus, to proactively look for specific phenotypic features that might redirect the genetic study towards TRPS.

This is not the first time that TRPS and PHP/PPHP have been misdiagnosed (15, 16). Even though resistance to PTH is a typical feature of PHP-Ia, it has already been reported in a patient with clinical characteristics of TRPS (16). The observations described 30 years ago in that 14-year-old boy could make more sense nowadays when looking at our TRPS case (patient 1), because, as stated before, partial resistance to PTH without associated hypocalcemia has also been found in some PHP-Ia patients (5, 11, 12).

The correct diagnosis of these patients leads to adequate follow-up and genetic counseling. In this case, these patients should not be treated and monitored in the same way as in PHP/PPHP (14) and they should receive genetic counseling appropriate for an autosomal dominant disease, without imprinting.

With the present report, we would like to highlight the main differences that could help distinguish the syndromes, in particular the sparse scalp hair and bulbous tip of the nose, which are both exclusive to and distinctive of TRPS (17). Regarding radiological findings, although they are not highly specific for PHP/PPHP [apart from shortening of the IV and V metacarpals and of the distal phalanx of the thumb (18, 19)], patients with TRPS present cone-shaped epiphyses at the phalanges, outcarving and deformation of the cones, which are more easily appreciated after epiphysis fusion (20, 21). These features have not been observed in patients with PHP/PPHP (19, 22).

Moreover, the very common skeletal deformities typically found in patients with TRPS may also be misdiagnosed with a rheumatic process even in young adult patients (23). Despite it not being the case, the hip and
knee arthralgias of patient 1, together with her morbid obesity and the polyarthrosis of her mother and brother, might also have distracted her physicians from the correct diagnosis. Therefore, while managing and controlling the global epidemic of obesity and in order to achieve the best possible long-term outcome for our patients and their families, clinicians should maintain a general vision of the whole clinical picture of each obese/overweight patient and still be able to identify the presence of distinctive phenotypic features of syndromes like those exclusive to TRPS that we have described in this report.

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