CLINICAL QUIZ (p254-255) ANSWER

After the new data was obtained, Pseudohypoparathyroidism (PHP)-Ia was suspected and later confirmed in the index patient, through the identification of a variant in the *GNAS* gene – c.1174G>A (p.E392K) in exon 13.

Molecular analysis was also requested for the family members who shared the same somatic features (Figure 4) (but whose posterior lab workup found no hormonal abnormalities) – they were found to also carry the same variant – in the case of her uncle and mother this was compatible with the hypothesis of a paternal-inherited variant – Pseudopseudohypoparathyroidism (PPHP) (Figure 5).

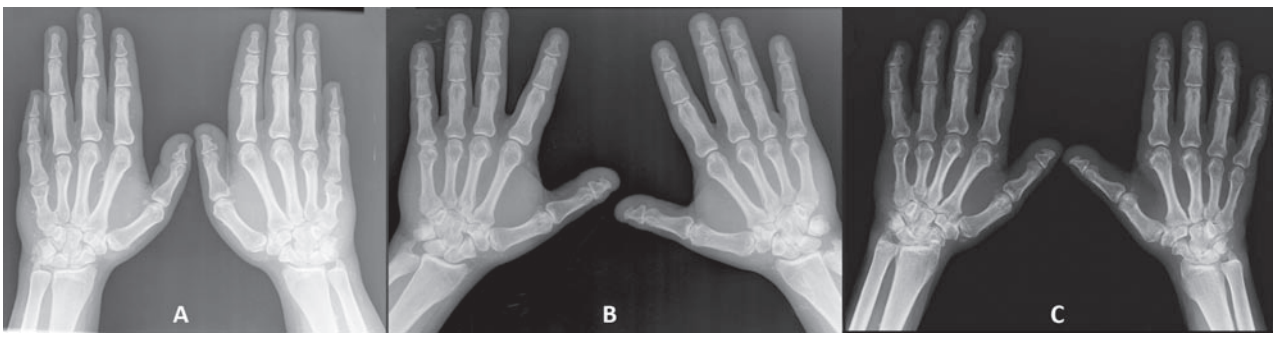

Figure 4 Hand X-ray of other studied family members showing brachydactyly (including a shortening of the distal phalanx of the thumb) and the presence of small ectopic ossifications. (A) Mother - shortening of IV and V metacarpals; (B) Uncle - shortening of V metacarpals; (C) Grandfather - shortening of metacarpals IV and V.

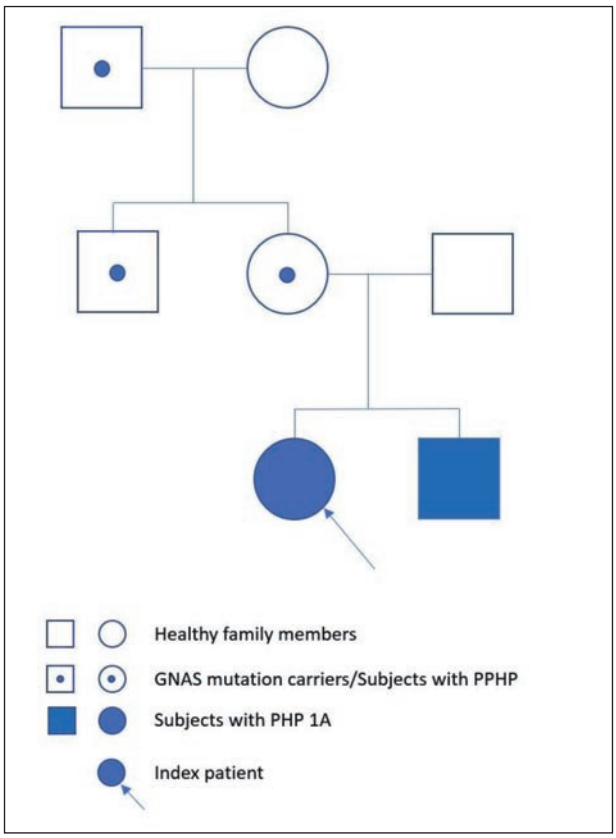

Figure 5 The subject's family chart/pedigree.

Clinical Features and Findings – PHP-Ia and PPHP

PHP encompasses a heterogenous group of disorders that differ in phenotype and aetiology but share end-organ resistance to PTH as their main characteristic.[1,2]

PHP-Ia, the most common subtype of PHP, is caused by pathogenic (inactivating) variants of the *GNAS* gene.[1-6] These variants are inherited in an autosomal dominant manner but, because of paternal imprinting, specific phenotypes are determined by the parental origin of the defective allele:[1-4,6,7]

- When subjects inherit the inactivating variant from their father, they only manifest somatic features (Albright's Hereditary Osteodystrophy (AHO)):[1-4,8] short stocky build, rounded face, brachydactyly and ectopic ossifications[1,2,5,6]– PPHP[2-4]* (Table 1).
- On the other hand, when maternally inherited, in addition to AHO characteristics, obesity and intellectual disabilities#, an impairment of hormonal signaling through stimulatory G-proteins occurs.[2-4,6,8] This causes PTH resistance (usually manifesting through hypocalcemia, hyperphosphatemia and elevated circulating PTH, in the absence of magnesium and renal function imbalances or vitamin D deficiency) and a variable degree of insensitivity to other hormones dependent on that signaling mechanism – TSH, growth hormone – releasing hormone, Gonadotropin, Somatotropin[1-8]– PHP-Ia[1,3,4,6,8] (Table 1).

Table 1 Disorders of GNAS inactivation - Phenotypes and genetic mechanisms

Phenotype	Endocrine defects	Clinical features	Parental origin of inactivated *GNAS* allele	Molecular defect
PHP- Ia	Multihormone resistance	AHO; early onseto besity	Maternal	Heterozygous ***GNAS*** pathogenic variant
PHP-Ic	Multihormone resistance	AHO	Maternal	Heterozygous ***GNAS*** pathogenic variant
PHP-Ib	PT H resistance; partial TSH resistance in some	Enhanced intrauterine growth; mild brachydactyly in some	Maternal	Heterozygous deletion of *STX16* or regulatory elements in ***GNAS*** complex locus (familial) Or Paternal 20q disomy or unknown epigenetic defect (sporadic)
PPHP	None	AHO; intrauterine growth restriction	Paternal	Heterozygous ***GNAS*** pathogenic variant
POH	None	Progressive heterotopic ossification extending to deep connective tissues	Paternal	Heterozygous ***GNAS*** pathogenic variant
Osteoma Cutis	None	Heterotopic ossification limited to dermis & subcutaneous tissues	Paternal	Heterozygous ***GNAS*** pathogenic variant

PHP - Pseudohypoparathyroidism; PPHP - Pseudopseudohypoparathyroidism; POH - Progressive Osseous Heteroplasia; AHO - Albright's Hereditary Osteodystrophy.
(Adapted from Haldeman-Englert CR, Hurst ACE, Levine MA. Disorders of GNAS Inactivation. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. [Internet] 2017).

* Rarely, in some families, a paternally inherited GNAS mutation can lead to a different condition - Progressive Osseous Heteroplasia (POH) – that is characterised by dermal ossification beginning in infancy, followed by increasing and extensive bone formation in deep muscle and fascia, usually without other AHO manifestations[2,6] (Table 1).

\# Some authors also describe the presence of obesity and intellectual disabilities in PPHP patients, considering them part of the AHO phenotype.[2,4,6,7]

In PHP-Ia, penetrance is complete but timing and severity vary significantly among affected individuals.[3] While evidence of TSH resistance is frequently present at birth (often detected on neonatal screenings) and can lead to the misdiagnosis of congenital hypothyroidism,[1-4,8] PTH resistance usually develops progressively during childhood.[2-4,6]

In comparison to the general population, higher rates of asthma,[2,8] sleep apnea (not only explained by obesity),[2,8] cataracts,[2] type-2 Diabetes Mellitus,[5] spinal stenosis,[2,3,5,8] carpal tunnel syndrome,[2,3,5,8] hearing loss,[5,8] decreased olfaction[2,5] and otitis media[2,5] have been reported in PHP-Ia patients.

A diagnosis based on clinical and biochemical findings should be confirmed by molecular genetic analysis.[2,3,8] The detection of a mutation in an index case allows a correct diagnosis and the possibility of predictive genetic testing in relatives.[6] It is appropriate to evaluate apparently asymptomatic first-degree relatives of an affected individual.[3]

Management of PHP-Ia

Early diagnosis and intervention as well as the establishment of a multidisciplinary follow-up are extremely important.[2]

Radiologic evaluation for brachydactyly is part of the condition's initial assessment.[1,3]

Endocrine essays are mandatory but may be very misleading due to the high variability in onset timing and severity of endocrine abnormalities among individuals, even within the same family.[1] Generally, these patients should be regularly monitored for serum PTH, calcium, phosphate[1,3] and calcefediol[2] as well as urinary calcium excretion.[1,3] Routine screening for any associated endocrinopathies is recommended – particularly hypothyroidism and hypogonadism.[1-3] Shorter intervals between assessments are recommended during childhood.[2,3]

In children, growth and pubertal development should be closely monitored.[1-3] Treatment of GH-deficient PHP-Ia patients with GH is still controversial[1] but should be considered.[3,8] Weight and body mass index should be monitored regularly to prompt early nutritional intervention when required.[1,2,8] Neurocognitive/neurodevelopmental assessments should be considered at diagnosis or pre-school age.[2]

Normocalcemia should be maintained in these patients through adjusted treatment with vitamin D metabolites such as calcitriol and, if necessary, oral calcium supplementation.[1,2] PTH target values should be the upper limits of the reference range – while excessive levels may adversely affect bone mineralization and the growth plate, PTH suppression may lead to renal calcifications and hypercalciuria.[1-3,8] If PTH levels are excessive, treatment should be considered even in normocalcemic patients.[1]

Treatment of hypothyroidism and hypogonadism is similar to any other non-PHP-Ia related form.[1-3]

There are no specific treatments for AHO manifestations – subcutaneous ossifications may be surgically removed if particularly incommodious.[1,3,8]

Case Report – Follow-up

Currently, at the of age 7, the index patient remains euthyroid and has maintained normal phosphocalcium metabolism under LT4, calcitriol, calcium carbonate and vitamin-D supplementation. Formal cognitive assessment revealed a normal (but borderline low) IQ.

Recently, the subject's mother delivered a 2360g male newborn. Because of his family history, phosphocalcium metabolism and endocrine studies were requested on the sixth day of life – while the former were within normal range for his age, a free-T4 level of 8.62 pmol/L and a TSH concentration of 13 mIU/L were detected. Therefore, he presented PHP-Ia in a similar fashion to his sister with hypothyroidism/TSH insensitivity developing first (before any phosphocalcium imbalances occurred). The same GNAS variant was detected in this newborn's genetic study confirming the diagnosis (Figure 5). He has been asymptomatic under LT4 substitution after 4 months of follow-up.

Take-home Messages

With this case report we aim at exemplifying the often-challenging diagnosis of PHP-Ia/PPHP – highlighting the importance of family history and of some particular clues found through physical and radiological exams. These findings support the request for endocrine assessments and, eventually, molecular analysis.

Knowledge of this disease's pathophysiology and intricate genetic patterns of inheritance along with careful study of the family's pedigree is therefore of paramount importance when managing these patients', their families' and their future offspring's conditions, allowing us to predict the phenotypes and therefore, future screening and therapeutic needs.

Early phosphocalcium metabolism and thyroid function assessments are recommended in these families' newborns.[2]

Declaration of Interest

The authors declare there are no conflicts of interest to disclose.

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