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Pseudohypoparathyroidism and its various phenotypes: three sisters with three different clinical presentations

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Abstract

Pseudohypoparathyroidism (PHP) is a heterogeneous group of hereditary disorders characterized by clinical and biological characteristics of resistance to parathyroid hormone (PTH) caused by impaired hormonal signalling via receptors that are coupled, through the α- subunit of the stimulatory G protein (Gsα). In some cases, resistance to other hormones (such as TSH, gonadotropins, GHRH and calcitonin) that have receptors coupled via Gsα is observed. A subset of patients with PHP are characterized by the variable expression of a collection of physical features, termed Albright hereditary osteodystrophy (AHO), which includes brachydactyly, rounded face, short stature, central obesity, subcutaneous ossifications, and variable degrees of mental retardation. These patients face a wide range of problems from early childhood to adulthood, which include potentially severe alterations in mineral metabolism, which could be associated with seizures; other endocrine deficiencies due to hormone resistance that lead to hypothyroidism, hypogonadism and GH deficiency; growth impairment independently of hormonal status; ectopic ossifications with potential severe limitation of mobility; skeletal issues and cognitive and psychomotor impairment.

Here we report three sisters affected by pseudohypoparathyroidism but with remarkably differences from each other in terms of phenotypic and clinical-auxological characteristics, a demonstration of how this disease is characterized by a very heterogeneous phenotype, even among patients carrying the same genetic alteration.

Key Words: pseudohypoparathyroidism, Albright osteodystrophy, PTH resistance, Gs-alpha protein

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Introduction

The condition of pseudohypoparathyroidism (PHP) refers to a heterogeneous group of hereditary disorders that have in common clinical and biological characteristics of resistance to parathyroid hormone (PTH) (1). PHP and related disorders are caused by molecular defects that impair hormonal signalling via receptors that are coupled, through the α- subunit of the stimulatory G protein (Gsα). The most common underlying mechanisms are de novo or autosomal dominantly inherited genetic mutations and/or epigenetic, sporadic or genetic-based alterations, within or upstream of GNAS, PRKAR1A, PDE4D or PDE3A. In some cases, resistance to other hormones (such as TSH, gonadotropins, growth hormone- releasing hormone (GHRH) and calcitonin) that

have receptors coupled via Gsα is observed.

Three types of PHP are distinguished: 1A, 1B and 1C. Patients with PHP1A and PHP1C are characterized by the variable expression of a collection of physical features, termed Albright hereditary osteodystrophy (AHO), which includes brachydactyly, rounded face, short stature, central obesity, subcutaneous ossifications, and variable degrees of mental retardation (2). Patients affected by PHP1B, on the other hand, typically show no evidence for AHO and, genetic analysis in these patients showed epigenetic defects into a region on chromosome 20q13.3 that comprises the GNAS locus (3). Very recently in a subset of patients with PHP and variable degrees of AHO, epigenetic defects of GNAS similar to those classically found in PHP-Ib patients were detected, suggesting a molecular overlap between PHP-Ia and PHP-Ib (4-8).

Mutations of PRKAR1A, PDE4D and PDE3A genes are involved in clinical conditions similar to classical PHP like Acrodysostosis type 1 and Acrodysostosis type 2 which must be investigated during diagnostic workup.

Clinical presentation and disease severity can vary considerably between affected individuals, even among patients carrying the same genetic alteration. Newborns and young infants usually present with unspecific features such as being born small for gestational age (SGA), early-onset obesity, or hypothyroidism. Later in life, growth failure, brachydactyly, obesity, and/or hypocalcemia leading to neuromuscular symptoms or even seizures often lead to investigations and identification of the underlying cause. The following major features should be present in order to diagnose a patient with PHP or a related disorder: PTH resistance and/or ectopic ossifications, and/or early onset (before 2 years of age) obesity associated with TSH resistance, and/or AHO (9).

The molecular analyses in the GNAS locus, although not yet able to identify all forms of PHP, can be a valid diagnostic support, as, in mutated cases, they allow the precise and definitive diagnosis of the disease and an appropriate management.

Case Report

Here we report three sisters affected by pseudohypoparathyroidism with remarkably differences from each other in terms of phenotypic and clinical-auxological characteristics (Table 1).

The oldest girl, came to our observation for the first time at the age of 4 years old for an occasional finding of hypocalcemia (Ca 7.4 mg/dl) and hyperparathyroidism (PTH 714 pg/ml).

The girl was positive for congenital hypothyroidism's neonatal screening and started replacement therapy with L-T4. Moreover she was followed in pediatric neuropsychiatry outpatient clinic for"mixed specific developmental disorder". At clinical examination she presented a shortness of the fourth metacarpus and round facies and had a stature at the lower limits of the norm (15°P) and

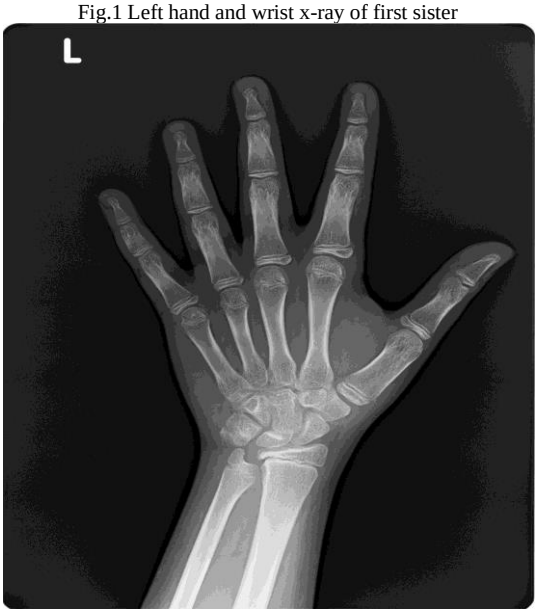
slight to moderate excess weight (27%).

Table 1. Clinical features of the three sisters

Clinical Features	First Sister	Second Sister	Third Sister
Short stature	✓ (severe)	-	✓ (mild)
Obesity	✓ (mild)	✓ (moderate)	✓ (severe)
Brachydactyly	-	✓	
Subcutaneous ossifications	-	✓	✓
Hypothyroidism	✓	✓	✓
Cognitive impairment	✓	-	-

Due to the aforementioned clinical situation, laboratory tests and concomitant neurocognitive disorder, pseudohypoparathyroidism was suspected and, therefore, a genetic investigation of the GNAS gene was performed, which however was negative in the first instance and supplementation with Vitamin D3 was started. Since then, the girl has undergone to six-monthly follow-up, during which was documented a progressive slowdown in the growth rate (height -2.21 SD at the age of 10) with basal dosage of GH and IGF-1 always within the normal limits. Pubertal development started regularly with normal gonadotropin values and she has never presented brachydactyly or subcutaneous calcifications, typical complications of the disease, as evidenced by the last left hand and wrist x-ray performed at the age of 10 years (Fig.1). Finally, a repeated study of the GNAS gene was carried out, the outcome of which is awaited.

Fig.1 Left hand and wrist x-ray of first sister



The second sister, at 6 years of age, came to our observation due to occasional diagnosis of acquired hypothyroidism. She presented a phenotypic picture characterized by various dysmorphisms such as: rounded facies, brachydactyly of hands and feet and subcutaneous ossification of the fifth finger of the left hand. In addition, there was a moderate excess weight (37%) with a height within the low normal limits for age (19° P). Our blood tests showed

hyperparathyroidism (PTH 783 pg/ml) and hyperphosphatemia (P 7.1 mg/dl). Therapy with L-T4 and Vit. D3 was started and molecular analysis of the GNAS gene was performed (still in progress). During the follow-up a progressive slowdown in the growth rate has been documented (height at 7°P at the age of 9), with basal dosage of GH and IGF-1 always within the normal limits. She has always maintained normal serum values of Ca and P in replacement therapy but she developed numerous subcutaneous calcifications documented by the last left hand and wrist x-ray performed at the age of 9 (Fig. 2).

Fig. 2 Brachydactyly of the IV and V metacarpus (red darts)Osteorarefaction and swelling of the metacarpal of the first finger (yellow dart).Osteosclerosis of the proximal phalanx of the V ray with disappearance of the proximal interphalangeal space (red circle)Large soft tissue calcifications close to the distal radius and ulna epiphysis (yellow circle)

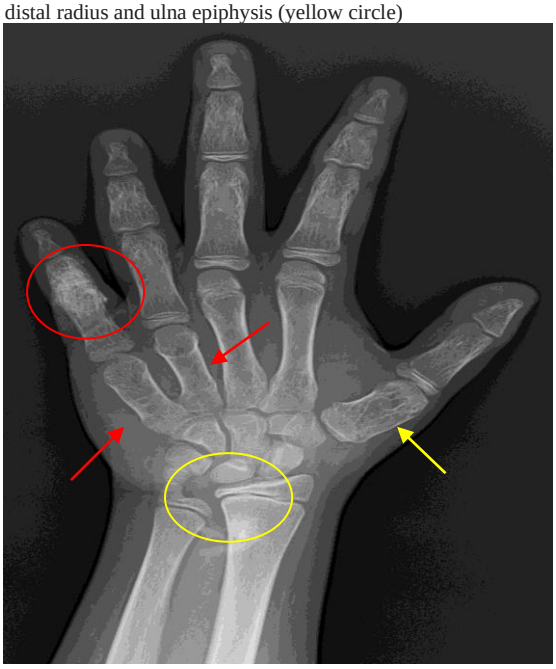
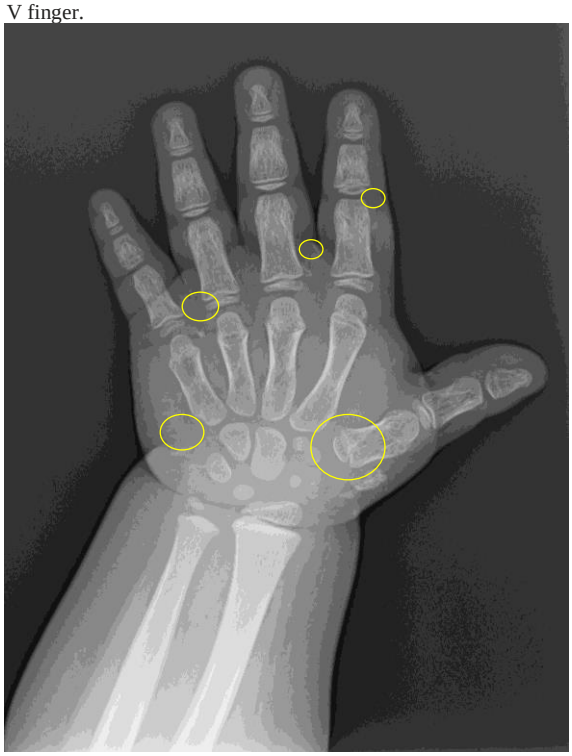


Fig.3 Calcifications in the context of soft tissues of the I, II and V finger.



Finally, the youngest of the three sisters, came to our observation at the age of 2, for congenital hypothyroidism already in replacement therapy. She had a significant statural deficit (-2.9 SD) and a moderate excess weight (27%), in the absence of evident dysmorphic features. Our blood tests showed hyperparathyroidism (361 pg/ml) with normal Ca and P serum levels. Therapy with Vit. D3 was therefore started and a study of the GNAS gene was performed (still in progress). After one year of follow-up there was a slight recovery in height (about 1 SD) but significant weight gain (43% overweight vs 27%) was observed. Therefore she also presented a pathognomonic radiographic picture with multiple subcutaneous calcifications (Fig. 3).

Discussion

We have described three sisters affected by PHP but with remarkably differences from each other in terms of phenotypic and clinical-auxological characteristics. They represent three emblematic demonstrations of how this condition is characterized by a very heterogeneous spectrum of

symptoms, clinical signs and complications, even among close relatives.

Once diagnosed, PTH resistance should be treated with activated forms of vitamin D, to increase the serum calcium levels and to thereby reduce PTH levels. The treatment of PTH resistance and functional hypoparathyroidism requires regular monitoring of serum levels of calcium, phosphorus, PTH (every 6 months in children and at least yearly in adults), monitoring of renal urinary excretion of calcium and renal function (3). Monitoring of serum levels of calcium should be more frequent in symptomatic individuals, during acute phases of growth, during acute illness and during pregnancy and breastfeeding, when dose requirements for active vitamin D metabolites or analogues might change.

Evaluation of thyroid function for early detection of TSH resistance is recommended in all patients with PHP at diagnosis and the indications to treat hypothyroidism, the dosage of levothyroxine and the therapeutic goals should be the same as for any patient with hypothyroidism or subclinical hypothyroidism (2).

Careful and regular monitoring of growth, skeletal maturation and GH secretion is therefore advised in all affected children, starting around the age of 3–6 years. Patients showing a GH deficiency should be considered for treatment with rhGH (9).

Dietary and lifestyle measures should be implemented at the time of diagnosis, irrespective of the body mass index, to prevent the development of obesity and metabolic complications (3).

Cognitive impairment has been reported in 40–70% of patients with PHP1A, therefore, these patients should be referred to a neuropsychologist for neurocognitive and/or behavioral assessment at diagnosis or at preschool age (9).

Resistance to gonadotrophins is more subtle than resistance to other hormones such as PTH and TSH. Clinically, patients may present with menstrual irregularities in girls, cryptorchidism in boys, and a blunted or absent pubertal growth spurt in adolescents (9).

The presence of subcutaneous ossifications should be investigated by careful examination during the follow-up. Physical therapy and meticulous skin care are the most important approaches for the prevention of development and/or progression of ectopic ossifications. Surgical excision should be considered in the presence of delimited, superficial lesions associated with pain and/or movement impairment (2).

In conclusion, it is clear that all patients with PHP and related disorders face a wide range of problems from early childhood to adulthood. This highly heterogeneous clinical picture renders, for all patients affected by PHP, a multidisciplinary approach mandatory, as very specialized expertise is required to manage each of the many clinical aspects and potential complications of PHP and related disorders.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was no supported by any grant.

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