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Pseudohypoparathyroidism and Albright Hereditary Osteodystrophy: A Case Report and Literature Review

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Abstract | **Case Report**

Introduction: Pseudohypoparathyroidism (PHP) is a rare disease and the first example of hormone resistance to be observed. It combines a particular morphotype, subcutaneous calcifications and bone and kidney resistance to parathyroid hormone. Other hormone resistances are possible. ***Case Presentation:*** Patient of 16 years old, had a progressive onset of right foot/ankle deformity at age of 12 years, then 6 months later contralateral ankle deformity, associated to Macrocrania, rounded forehead, enlarged nose, micrognatism, short neck, brachydactyly, deformities, Genu valgum. Workup; corrected hypocalcaemia 46.9mg/l hyperphosphaemia 66mg/l high PTH 1739pg/ml, normal renal function. Diagnosis retained: Pseudohypo-parathyroidism Type 1A or 1C associated with Albright hereditary osteodystrophy (AHO), genetic confirmation in progress. ***Discussion & Conclusion:*** PHP is a rare autosomal dominant inherited disorder of variable penetrance and expression, most severe when maternally inherited. Genetic studies have identified inactivating mutations in Gs-alpha, encoded by the GNAS gene, responsible for several phenotypes. Management consists of multidisciplinary follow-up and early and specific interventions. Prognosis is variable, normal life expectancy in mild forms, significant morbidity and mortality in severe forms.

Keywords: Pseudohypoparathyroidism, Albright hereditary osteodystrophy, Management, Prognosis.

INTRODUCTION

Pseudohypoparathyroidism or Albright Hereditary Osteodystrophy is the first example of hormone resistance observed in human pathology. Albright, in 1942, made the first description [1, 2]. It is associated with hypocalcemia, hyperphosphatemia, and increased circulating parathyroid hormone (PTH) levels [3].

This rare genetic disease combines a particular morphotype, subcutaneous calcifications and bone and kidney resistance to parathormone, other hormonal resistances may also be present [1, 4]. It is linked to a mutation in the GNASI gene, located at 20q13.2q13.3 [3]. The same mutation is responsible for several phenotypes depending on the parental allele inherited, PHP type 1 a, 1 b, lc, pseudo-PHP (type 2) but also a related disease, Progressive Bone Heteroplasia [1].

In this article, we present a case of a 16 years old patient with PHP type 1A or 1C and a literature review.

CASE PRESENTATION

Female Patient of 16 years old was born via normal vaginal delivery at full term. She was appropriate for gestational age, and had a normal psychomotor development. Her target height is 150cm. She had her menarche at 13 years old; she was diagnosed with hypothyroidism 3 years before. The patient presented progressive onset of right foot/ankle deformity at age 12 years, then 6 months later contralateral ankle deformity. Clinical examination noted a negative shvostek sign, BMI 20.4kg/m2, Tanner S5P4, Macrocrania, rounded forehead, enlarged nose, micrognatism, short neck, brachydactyly, deformities of ankles, wrists and clavicles and genu valgum (figure1).

Paraclinical exams showed a corrected hypocalcaemia 46.9mg/l hyperphosphaemia 66mg/l high PTH 1739pg/ml, normal renal function, TSH 9.3mui/l, Cortisol 13.5ug/dl, LH 8.2ui/l, FSH 9.9ui/l, Estradiol 5ng/l.

X-ray exam noted a bone age between 13 and 14 years for a chronological age of 16 years and 10 months. Brachymetacarpia especially in the third metatarsal on the left and the fourth on the right and Brachymetatarsia. Incuvation of the distal part of the radius and femur, no subcutaneous ossifications detected (Figure 2). On cervical Ultrasound a multinodular goiter with parathyroid nodule 18x9x6mm was diagnosed, but 99mTc-sestamibi Parathyroid scintigraphy showed no fixation. abdominopelvic ultrasound was normal. Whole body bone densitometry found osteopenia (Figure 3).

Diagnosis retained: Pseudohypo-parathyroidism Type 1A or 1C associated with AHO (genetic confirmation in progress). The management consisted on the correction of severe hypocalcaemia by intravenous fluids, followed by oral supplementation of calcium (2g per day) and Vitamin D (Alfa calcidiol 2ug per day) and administration of L-thyroxine 50ug per day. Orthopaedic surgery for bone deformities and parathyroid surgery are planned.

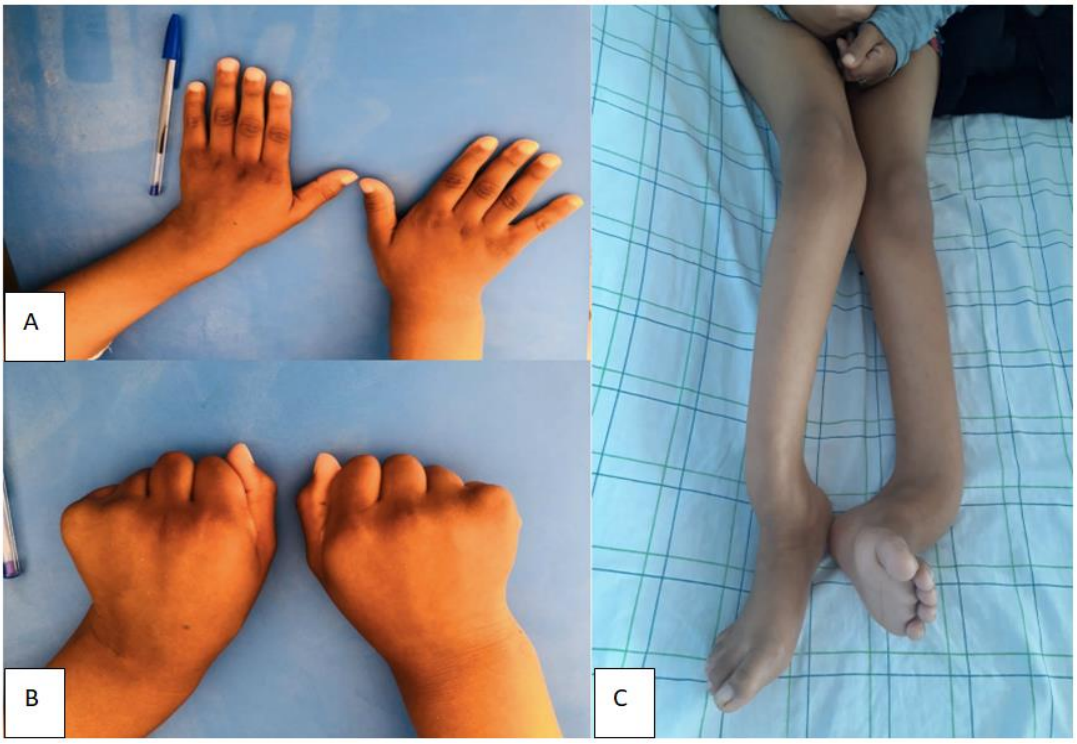

Figure 1: A-B: brachydactyly. C: Genu valgum and deformities of ankles

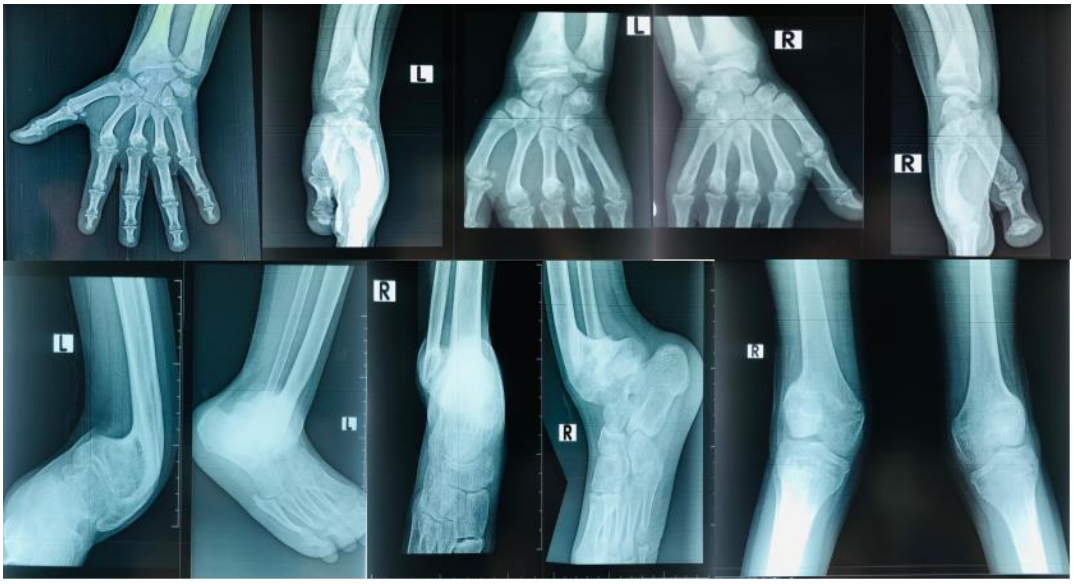

Figure 2: X-ray exams of our patient

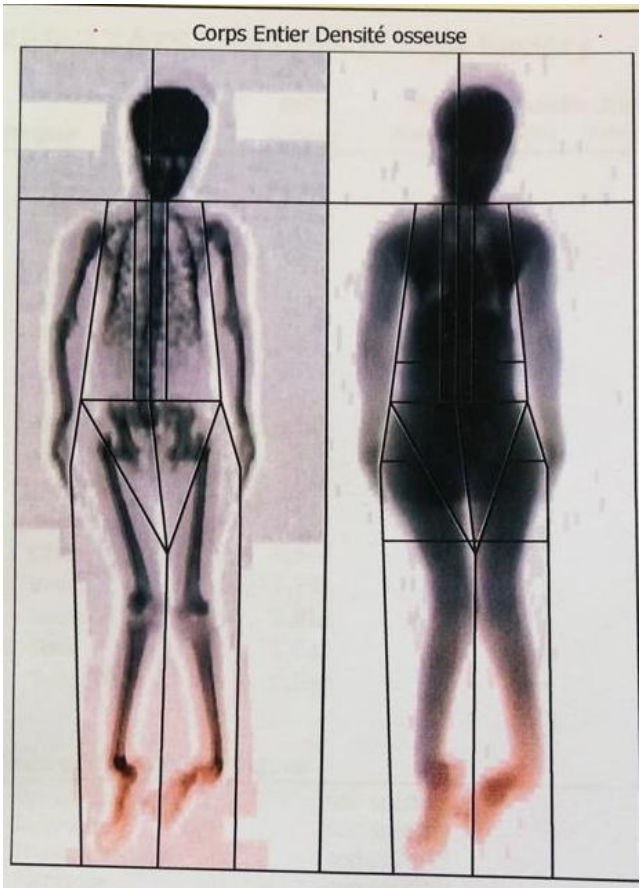

Figure 3: Whole body bone densitometry of our patient

DISCUSSION

PHP is comprised of a heterogeneous group of rare diseases caused by different genetic and/or epigenetic defects of the PTH/PTHrP signaling pathway leading to peripheral resistance to the action of PTH, it has an estimated prevalence of 0.79/100000 inhabitants [5, 6]. It is classified into different subtypes based on the phenotype, the hormonal resistance pattern, the genetic defect and the renal response to exogenous PTH infusion [6].

The phenotype is related to the presence or absence of physical features of AHO. It's a hereditary condition that generally occurs during late childhood, due to defects in chondrocyte and osteoblast differentiation, early closure of growth plates, brachydactyly, a short stature, and development of ectopic ossifications [6-8].

Hormone resistance is determined by the resistance to other hormones dependent on the Gsα protein system, such as TSH, gonadotropins or GH [6, 8]. Pseudo-PHP presents isolated typical AHO phenotype without alterations in the phosphocalcic profile since there is no resistance to the action of PTH [6, 9].

The diagnosis of PHP is made on the basis of clinical features and endocrine outcomes, but if possible, it should be confirmed by molecular genetic testing.

Biological profile of PHP is characterized by hypocalcemia and hyperphosphatemia, with normal renal function and elevated serum concentrations of PTH [6, 9]. In PHP, the proximal renal tubule is the main site of resistance to PTH, as a direct result, hyperphosphatemia and low concentrations of 1,25 dihydroxyvitamin D are observed. PTH responses in the bone and distal renal tubule are preserved; high levels of PTH could partially prevent symptomatic hypocalcemia by mobilizing calcium from the bone and increasing renal calcium reabsorption [6, 10].

The diagnostic approach of our case was made based on hypocalcemia, which suggests the diagnosis of PHP when associated with hyperphosphatemia and elevated PTH. Although urinary cAMP measurement was not carried and genetic studies are in progress in our patient, it was possible to achieve an initial approximation based on the phenotype and the hormonal resistance profile. Our case presents phenotypic features of AHO, the most probable diagnosis is PHP type 1A or 1C, genetic confirmation is on progress. Identification of the causative genetic or epigenetic defect is crucial for predicting the natural history of the disorder, disease inheritance, and

affording appropriate medical and genetic counseling [2].

A coordinated and multidisciplinary follow-up and early specific intervention is necessary for efficient therapeutic management of PHP. No specific treatment has been described. The administration of active metabolites of vitamin D, ideally calcitriol, with or without oral calcium supplement and with dose adjustment until achieving a calcium level in the normal range is recommended [6, 11]. Patients with hypothyroidism due to TSH resistance should receive oral thyroxine and undergo regular assessment of their thyroid function [4, 12]. Patients with PHP and short stature or decreased growth velocity should be evaluated for growth hormone (GH) deficiency [2, 12]. Dietary and lifestyle measures should be implemented at the time of diagnosis, to prevent the development of obesity and metabolic complications. The treatment of ectopic ossifications is challenging, surgery may be indicated to remove the ossifications that cause pain and/or irritations [2]. Depending on the functional consequences of skeletal feautures, the patient might require corrective orthopaedic surgery [12]. Prognosis is variable, normal life expectancy in mild forms, significant morbidity and mortality in severe forms.

CONCLUSION

Multidisciplinary approach is mandatory to manage the different clinical aspects and potential complications of PHP. The identification of the genetic defect causing PHP is fundamental to perform a conclusive diagnosis, allowing an appropriate genetic counseling.

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