A Case Report of a 14 Year Old Male with Pseudohypoparathyroidism Associated with Multiple Hormonal Resistance

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Abstract Albright hereditary osteodystrophy (AHO) is a rare hereditary metabolic disorder that may or may not be associated with resistance to parathyroid hormone (pseudohypoparathyroidism) or other hormones. The disorder is commonly characterized by a constellation of dysmorphic physical features and with biochemical levels that demonstrate hypocalcaemia and hyperphosphatemia. We report here a clinical case of a 14 year old male with AHO and we discuss his clinical features, radiographic and laboratory findings along with treatment.

Keywords Albright's hereditary osteodystrophy · Pseudohypoparathyroidism · Hormonal resistance · GNAS1 · Hypocalcaemia · Hyperphosphatemia

Introduction

Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders clubbed together with resistance to parathyroid hormone (PTH) in common. Albright's hereditary osteodystrophy is a rare metabolic disorder with clinical presentation of parathyroid (PTH) resistant hypocalcaemia, hyperphosphatemia along with an unusual constellation of developmental and skeletal defects [1]. A Japanese study estimated prevalence of the disorder to be 7.2 per million only. First described by Fuller Albright in 1942,

pseudohypoparathyroidism is a clinically dysmorphic syndrome characterized by developmental and skeletal defects that include short stature, rounded face, shortened fourth metacarpals and other bones of the hands and feet, obesity, dental hypoplasia, soft-tissue calcifications/ossifications. Although the features are characteristic they may vary, as many of the patients usually show unremarkable phenotypic features. Skeletal defects are routinely confirmed by doing X-rays of the hands and feet. The 4th and the 5th metatarsals generally show brachydactyly and subcutaneous ossifications [2]. Biochemically patients with AHO present with hypocalcaemia, hyperphosphatemia and elevated PTH levels.

Etiology

AHO is a rare autosomal dominant disorder with varying clinical presentation depending on the mode of inheritance of the mutated allele, i.e., either maternal or paternal.

The major molecular defect causing the syndrome lies in the GNAS1 gene, which encodes the $G_{s\alpha}$ —subunit of the G_s complex. The $G_{s\alpha}$ coupled receptors are involved in signal transduction of several peptide hormones [3]. The varying molecular defects in this gene result in three different forms of the disease called PHP type 1a, type 1b and pseudo-pseudo-hypoparathyroidism. Heterozygous mutations inherited from the maternal allele are associated with the clinical loss of function and hormonal resistance wherein administration of PTH fails to produce phosphaturia or stimulate renal production of cyclic adenosine monophosphate (cAMP) [4]. Patients with PHP type 1a show—both phenotypic and biochemical features due to inactive or decreased amounts of $G_{s\alpha}$. Whereas, the milder phenotype of AHO, pseudo-pseudo-hypoparathyroidism, presents only with phenotypic features and PHP type 1b

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Fig. 1 Bilateral brachydactyly **a** Of the hands with shortening of all metacarpals. **b** Of the feet with shortened fourth and fifth toes on both feet

Fig. 2 Radiographs of the patient **a** Radiographs of both hands showing brachydactyly due to shortening of all metacarpals **b** Radiographs of both feet showing bilateral shortening of the fourth and fifth

metatarsals. **c** Lateral radiograph of the skull showing thickened calvarium and open bite phenomenon

with none and only has signs of PTH resistance confined to renal parenchyma.

Herein, we report a case of AHO with characteristic biochemical, developmental and skeletal defects.

Case Report

A 14 year old male patient presented to our endocrine outpatient clinic primarily with complaints of short stature. The patient gave history of episodes of seizures a week prior to being seen in our outpatient department and had been admitted to a local hospital for the treatment. On biochemical evaluation the cause for the seizures was discerned to be due to hypocalcaemia. He was treated with I.V calcium and referred to us for further evaluation. Chvostek's and Trousseau's sign were both positive. He was a product of non-consanguineous marriage with a normal birth and developmental history. On further enquiry, his past medical history revealed that he was hypothyroid since the age of 2 and is replaced with 50 µg of thyroxine. On taking the family history, we found that the patient is the younger of two siblings and we identified that his elder sister 18 years of age is of normal height and

weight for her age and is medically normal. However, we found on examination that his mother had a short 4th toe on her left foot.

On physical examination, the boy weighed 57 kg, measured 141 cm in height and at Tanner stage-4 of puberty corresponding to 12.5–14 years. He had a round face, short stubby fingers, depressed 4th knuckle on both hands (Fig. 1a) and brachymetatarsia of the 3rd & 4th toes on both feet (Fig. 1b). Café au lait spots were noted on his back and right side of his thigh. His penile length was 6 cm (normal 10 cm), testicular volume: is 12 ml bilaterally (normal—12–20 ml). X-rays of both the upper limbs, lower limbs and skull were taken. Roentgenogram pictures of limbs revealed bilateral short metacarpals (Fig. 2a) and short 3rd, 4th, 5th (Fig. 2b) metatarsals. Lateral view of skull radiograph showed thickened calvarium and an open bite (Fig. 2c). Mothers radiograph of left foot also showed short 4th metatarsal (Fig. 3). Bone mineral density examination showed a generalized osteopenia. Nuclear imaging confirmed presence of a severe degree of osteoporosis (Fig. 4). His baseline endocrine and biochemical values are shown in Table 1. All routine biochemical parameters are analyzed on Roche fully automated biochemistry analyzer c311 with dedicated reagents. All hormonal analysis is

Fig. 3 Radiograph of the mother showing short left fourth metatarsal

Fig. 4 Tc 99m MIBI scan of the patient showing generalised osteoporosis

done by ECLIA on Roche e411 except for DHEAS, IGF-1 and Growth Hormone which were analyzed by ECLIA on Immulite 2000 (Seimens fully automated Immunoassay analyzer).

He was treated with calcium supplements and calcitriol. On follow up, serum calcium levels and urinary calcium/creatinine were monitored to achieve good calcemic levels. Complete blood count, blood sugar levels, and liver and renal function tests were normal. We also evaluated the mother's biochemical and hormonal profile and found that

Table 1 Baseline biochemical and hormonal profile

Analyte	Value	Reference range (age matched)
RBS (mg/dl)	84	<140
Calcium (mg/dl)	6.0	8.5–10.8
Phosphorus (mg/dl)	6.9	2.5–5.5
Alkaline phosphatase (IU/ml)	536	150–350
Sr creatinine (mg/dl)	1.0	0.7–1.4
Sr sodium (mmol/l)	140	136–146
Sr potassium (mmol/l)	5.1	3.5–5
Urine calcium (mg/dl)	230	50–250
Urine phosphorus (mg/dl)	106	5–189
Urine sodium (mmol/l)	110	41–115
Urine potassium (mmol/l)	50	40–80
Hormonal Assays:		
Parathyroid hormone (pg/ml)	225	15–65
25(OH)VitD (ng/ml)	6.95	30–100
Free T4 (ng/dl)	1.11	0.89–1.76
TSH (μ U/ml)	16.96	0.35–5.50
FSH (U/L)	1.7	1.4–18
LH (U/L)	2.08	1.5–9.3
Testosterone (ng/dl)	92.6	220–800
IGF-1 (ng/ml)	71.5	108–558
DHEAS (μ g/ml)	<15	65–560
GH stimulation test (ng/ml) 0 min	1.1	Up to 10
30 min (ng/ml)	1.5	
60 min (ng/ml)	1.8	>10 after peak stimulation
Cortisol (μ g/dl)	10.1	4.3–22.4

she had normal thyroid function tests, normal FSH and LH levels as shown in Table 2. However 1,25 dihydroxy Vitamin D and PTH induced cAMP levels could not be estimated due to non availability of tests and financial constraints.

Treatment

The patient was treated with calcium supplements (Maxi-trate 500 mg bd) and 1,25 dihydroxy Vitamin D supplementation (caldikind sachets 1/week for 8 weeks) with regular follow ups.

Discussion

The constellation of typical phenotypic features of pseudohypoparathyroidism with resistance to parathyroid hormone is collectively termed as AHO [5]. These patients demonstrate concomitant hypocalcaemia and hyperphosphatemia despite elevations in the concentration of

Table 2 Baseline biochemical and hormonal profile of the mother

Analyte	Value	Reference range (age matched)
Calcium (mg/dl)	8.0	8.5–10.8
Phosphorus (mg/dl)	4.1	2.5–5.5
Alkaline phosphatase (IU/ml)	310	150–350
Hormonal Assays:		
Parathyroid hormone (pg/ml)	40	15–65
Free T4 (ng/dl)	1.08	0.89–1.76
TSH (μ IU/ml)	3.99	0.35–5.50
FSH (U/L)	10.33	2.5–10.2
LH (U/L)	10.48	1.9–12.5
Prolactin (ng/ml)	5.71	2.80–29.2
Estrogen (pg/ml)	44.68	18.9–246.7

parathyroid hormone in plasma. Hypocalcaemia develops due to loss of the bone resorptive action of parathyroid hormone resulting in defective mobilization of calcium from bone and reduced GIT absorption of calcium. Our case represents a unique case of AHO with characteristic biochemical and phenotypic findings, wherein he demonstrates frank hypocalcaemia and hyperphosphatemia with elevated parathyroid hormone levels. He additionally showed resistance to other hormones that are reflected with distinct decreases in GH, IGF-1, testosterone and DHEAS, whereas FSH, LH and cortisol levels, although not decreased, were found to be at the lower side of the normal for his age matched reference range. Aside from the biochemical findings he also showed characteristic phenotypic features of AHO that include obesity, shortened metatarsals, and shortening and broadening of distal phalanges. His mother was also found to have shortened metatarsal on her physical evaluation that indicates a probable maternal mode of inheritance in our patient. Primary hypothyroidism and reproductive dysfunction are a common occurrence in these patients and women may have delayed puberty, oligomenorrhea, and infertility [6]. In our patient we did in fact note features of hypothyroidism, decreased penile length with reduced testicular volume. A decrease in the levels of reproductive hormones, growth hormone, IGF-1 and nocturnal enuresis may thus suggest decreased activity of $Gs\alpha$ at the level of pituitary, that warrants further analysis. The $Gs\alpha$ coupled receptors are known to participate in signal transduction of several peptide hormones, glycoproteins, catecholamines and neurotransmitters through stimulation of adenyl cyclase to produce cAMP [3]

which acts as a second messenger for these hormones. Heterozygous mutations in the gene (GNAS1), that encodes $Gs\alpha$, when inherited from the maternal allele are associated with the clinical loss of function and hormonal resistance. Patients with inactive or decreased amounts of $Gs\alpha$ showing phenotypic and biochemical features are diagnosed as PHP type I, similar to our case.

The patient was managed symptomatically with intravenous calcium initially and he was encouraged to follow up biannually with measurement of serum calcium, phosphorus, parathyroid hormone and thyroid-stimulating hormone levels, along with 24-hour urinary calcium–creatinine ratio for titration of therapy.

Conclusion

The important clinical features in our case are symptomatic hypocalcaemia, hyperphosphatemia with short fourth and fifth metacarpals, elevated PTH levels, hypothyroidism and radiological findings typical of AHO. Only pseudo-hypoparathyroidism includes both the features hypocalcaemia and short metacarpals, therefore, supporting our diagnosis of pseudo-hypoparathyroidism in this 14 year old boy. Our case thus presents as a rare case of AHO with multiple hormonal resistance with typical phenotypic expression.

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