Clinical Brief

Albright's Hereditary Osteodystrophy

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Abstract. Albright's hereditary osteodystrophy is a rare inherited metabolic disorder characterized by a typical phenotype. It may be associated with or without resistance to parathyroid hormone (pseudohypoparathyroidism). Both forms may co-exist in the same family. Pseudohypoparathyroidism Type 1 and Pseudo-pseudohypoparathyroidism occur as a consequence of reduced erythrocyte membrane coupled with Gs alpha activity. We report here the variable inheritance of hormone resistance in the presence of characterstic phenotype and reduced Gs alpha activity in the same family.
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Albright hereditary osteodystrophy (AHO) is a metabolic disorder, first described by Fuller Albright in 1942 and is also called acrodysostosis.[1] It is characterized by a constellation of physical features including short stature, brachydactyly, osteoma cutis, obesity, rounded facies; and in some cases, mental and developmental anomalies.[2] Within members of the kindred, AHO may present alone pseudo-pseudohypoparathyroidism (PPHP), or in association with resistance to other hormones (e.g., Parathormone [PTH], gonadotropins and TSH), when it is called pseudohypoparathyroidism (PHP). One of the important causes is reduced Gs alpha activity, which is present in PHP type 1a and PPHP. Here is reported a family where the sibs had PHP and the mother had PPHP and all showed decreased Gs alpha activity.

CASE REPORT

A nine-yr-old female was brought with complaints of inability to gain height and recurrent dental problems in the form of tooth decay, tooth loss and malalignment, for which repeated dental consults were sought. There was no history of diarrhea, urinary complaints, constipation, excessive somnolesence and recurrent fractures. She was the product of a non-consanguinous marriage and was delivered at home with no significant complaints in the neonatal period. Poor growth velocity had also been documented in the elder male sibling at a private tertiary care center. Global development delay was present during childhood, and presently her scholastic performance was poor.

She had a rounded chubby face, blue sclera and short stubby hands and feet (Fig 1,2). Her height was 82% of expected; weight was 58% of expected, head circumference 92.5% of expected and weight for height was 92% of expected. Upper to lower segment ratio was 1 (normal for age) and arm span was normal for height. Mid-parental height was 147 cm; her BMI was 14.1. Oral cavity examination revealed multiple hypoplastic, carious and malaligned teeth with exposure of dentine. Systemic examination was normal. Her sexual maturity rating (SMR) was Tanner's stage I. Examination of the elder sibling revealed short stature with short stubby hands and feet and shortening of the little finger. The mother had normal stature and body habitus but short of left ring finger and both fourth toes.

Fig. 1. Child with round pudgy face.

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Investigations revealed normal blood counts as well as normal LFT, KFT, chest X-ray and urine examination. Skeletal survey showed osteopenia, short metacarpals and metatarsals with a bone age of 5 years and 2 months (Greulich-Pyle method).Thyroid function test showed a decreased serum T4, a normal T3 and an elevated TSH.

The combination of short stature, concordant height and bone age in the presence of hypothyroidism, dental anomalies and osteopenia prompted estimation of serum calcium, phosphorus and alkaline phosphatase. Hypocalcemia (S. Ca^{2+} 4.2 mg / dl), hyperphosphatemia (S. PO_4^{3-} 6.7 mg / dl) and normal alkaline phosphatase (15 KAU) were suggestive of hypoparathyroidism. Serum parathyroid hormone levels, however, were grossly elevated (529.4 pg / ml). This biochemical profile was indicative of resistance to parathyroid hormone (Pseudohypoparathyroidism). The elder sib's investigations revealed a calcium of 5.6 mg / dl, phosphate level of 6.8 mg / dl, TSH of 12 mIU / ml and PTH levels of 646.6pg / ml. Investigation of the mother revealed normal calcium, phosphate, alkaline phosphatase and parathyroid levels. The mother's skeletal survey revealed short 4^{th} metacarpal on the left side and bilateral short 4^{th} metatarsals (Fig 3). The biochemical profile along with the characterstic phenotype of the index case and family members was typical of Albright's hereditary osteodystrophy (AHO). The index case and the elder sib had pseudohypoparathyroidism and the mother had pseudo-pseudohypoparathyroidism. Resistance patterns to other hormones were studied. Growth hormone provocative test was negative, suggesting growth hormone deficiency; however, the serum levels of FSH, LH and prolactin were normal. Further subtyping was deferred due to nonavailability of urinary cyclic AMP excretion. The Gs alpha activity in the erythrocyte membranes in the index case was 49.2%, in the sib 54.8% and in the mother 59%.

CT cranium revealed calcification of bilateral basal ganglia and grey-white matter junction of both frontal lobes. Slit lamp examination showed peripheral cortical cataract in both eyes. Oral Pantogram showed enlarged pulp chambers with irregular and hypoplastic occlusal surfaces of permanent molars (Fig 4). The index case had an Intelligence Quotient of 43, while the elder sibling had an Intelligence Quotient of 67.

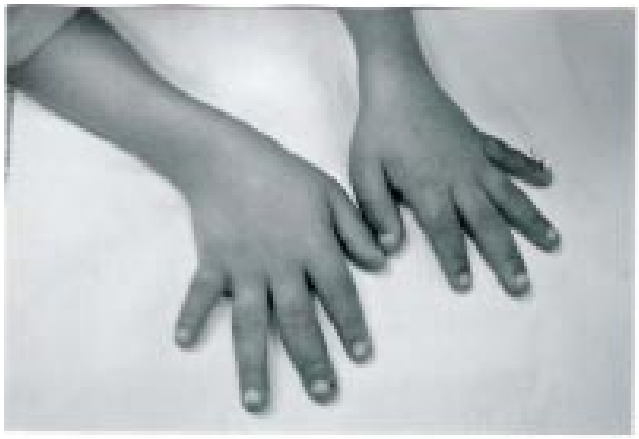

Fig. 2. Photograph showing short stubby hands

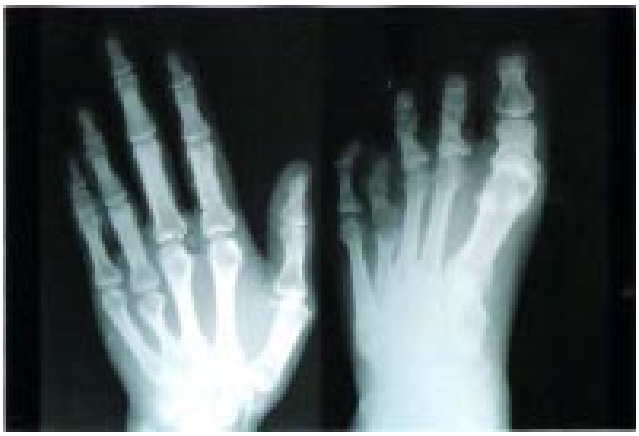

Fig. 3. Radiograph of mother showing short fourth metacarpal and metatarsal

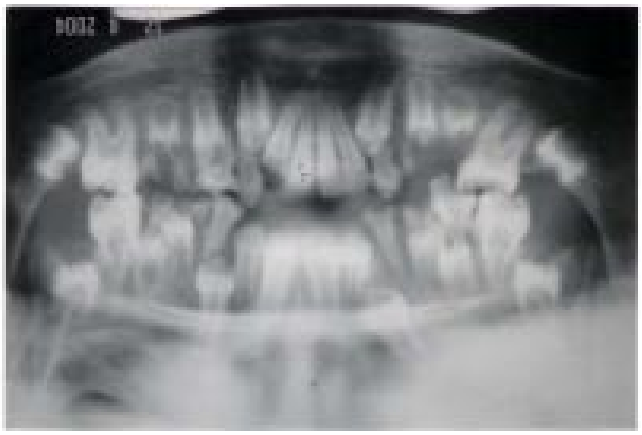

Fig. 4. Oral pantogram showing malocclusion and hypoplasia

Both the index case and the sib were initiated on thyroxine and calcitrol along with calcium supplementation. Six months after diagnosis the urinary calcium and phosphorus excretion measured in 24 hours sample are within the normal range.

DISCUSSION

Pseudohypoparathyroidism (PHP) is an inherited metabolic disorder characterized by end organ resistance to the action of PTH. PTH maintains serum calcium levels by promoting bone resorption, enhanced distal tubular resorption of calcium and increased synthesis of 1, 25 hydroxy vitamin D, thereby causing enhanced intestinal calcium absorption.

Resistance to PTH, therefore, leads to hypocalcemia and hyperphophatemia. This combination of findings may also be found in phoshate overload (dietary, massive

TABLE 1. Typical Abnormalities in Pseudohypoparathyroidism and Pseudo-pseudohypoparathyroidism

Type	Appearance	S Ca	S Po4	PTH	Response UcAMP / Po4	Defect
Ia	AHO	↓/N	↑	↑	--/--	Gsα
Ib	N	↓/N	↑	↑	--/--	PTH receptor
IC	AHO	↓/N	↑	↑	--/--	Catalytic subunit
II	N	↓	↑	↑	↑/-	Protein Kinas Phosphate system
PPHP	AHO	N	N	N	↑/↑	Gsα

cellular breakdown and renal failure). Since dietary overload is restricted primarily to the neonatal age group and increased cellular turnover is also limited to selected specific clinical settings *eg.* cancer chemotherapy, the main differential remains secondary hyperparathyroidism. Alkaline phosphatase levels are usually increased many fold in this condition with the characteristic appearance of osteitis fibrosa cystica.

PHP is often associated with a characteristic phenotype known as Albright's hereditary osteodystrophy. The phenotype consists of a rounded face with a short, stocky built. There is brachydactyly with dimpling of the dorsum of hand. Shortening of the digits only rarely involves the second digit (both upper and lower limb), so that the ring finger is shorter than the index finger. The abnormalities of the 4th and 5th metacarpals and metatarsals are characteristic. Dental anomalies are present in the form of enamel defects, hypoplasia and caries.[3] Thickened calvaria, short and wide phalanges with metastatic calcification and exostoses may also be present. Skeletal anomalies include *genu valgum* and *radius curvus.* Mild mental retardation, basal ganglia calcification and lenticular cataracts are found later in life. In a series reported by Papaionnou, the incidence of diagnostic features is as follows: short metacarpals or tarsals (92%), short stature (76%), round face (71%), mental retardation (64%), obesity(61%), ectopic calcinosis (35%) and exostosis (23%).[4]

Subclinical hypothyroidism, diabetes, delayed puberty and oligomenorrhea reflect the presence of hormone resistance in the same family.[5] In some patients this phenotype is found without biochemical evidence of PTH resistance. This has been termed as pseudo-pseudohypoparathyroidism (PPHP). PPHP is often found in kindreds affected with PHP, and hypocalcaemia usually occurs with increasing age. PHP has three subtypes. Patients with PHP Ia have AHO phenotype, resistance to G-protein-coupled hormones, attenuated response in urinary phosphate and CAMP excretion after intravenous infusion of synthetic PTH (Ellsworth Howarth test, standard procedure as detailed elsewhere [6]) and a decreased G_sa activity. The disorder is inherited in an autosomal dominant manner. Patients with PHP Ib do not have AHO phenotype, and resistance to other G-protein-coupled hormones is absent. Patients with PHP Ic have similar AHO phenotype, and resistance to other G-protein-coupled hormones is associated but the defect appears to be in the adenylate cyclase receptor. Ellsworth Howarth test cannot differentiate between the three. In PHP II, the phenotype is normal but the excretion of CAMP is elevated in basal state as well as after stimulation with PTH. These have been depicted in table 1.

The age and mode of presentation are unpredictable. Some patients present with classical symptoms of hypocalcemia (tetany, seizures) during infancy, while others present with short stature during later life. The dysmorphic features may be absent at presentation and may evolve during childhood. Metacarpal and metatarsal abnormalities may not appear till mid-childhood. Intracranial calcifications and cataracts appear only during late childhood. There is considerable phenotypic variability of the disease in the same family and the same generation. The same subtypes are present in the same generation but may differ in the family. Hence, a high index of suspicion should be kept while investigating short stature and hypocalcemia, and an extended family examination may offer an important clue to the diagnosis.

Treatment consists of controlling hypocalcaemia and the attendant signs and symptoms of tetany and seizures. This is best achieved by careful administration of calcium and active vitamin D, cholecalciferol, which must be monitored closely. Normocalcemic patients with PPHP should be evaluated regularly for development of hypocalcemia and cataracts, and their physical and mental progress should be followed closely. Excision of asymptomatic foci of cutaneous ossification is not usually necessary but may be required for individual lesions causing cosmetic disfigurement.[7] In some patients with AHO, hypothyroidism may be an early manifestation, and the diagnosis of AHO should be considered in the evaluation of childhood primary hypothyroidism, particularly, if there is no goiter, hypoplasia or ectopic thyroid tissue.[8]

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