A Rare Case of Hypocalcaemia

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ABSTRACT

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Hypocalcaemia evaluation is very important, as it may be seen most often in practice. We are reporting a case Pseudohypoparathyroidism Type Ia, which is one of the very rare causes of hypocalcaemia. The patients present with distinctive skeletal and developmental defects (Albright's hereditary osteodystrophy) along with decreased calcium, hyperphosphatemia and high parathyroid hormone levels.

Keywords: Hypocalcaemia, Pseudohypoparathyroidism, Albright hereditary osteodystrophy

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INTRODUCTION

Hypocalcaemia is one of the common problems in day to day clinical practice, which should be evaluated in detail. Pseudohypoparathyroidsm is one of the rare cause hypocalcaemia, in which patients will have Albright's hereditary osteodystrophy: short stature with other distinctive skeletal and developmental defects along with hyperphosphatemia, increased parathyroid hormone levels.

CASE REPORT

Eighteen year old female presented with complaints of numbness of all four limbs since one week, initially on the lower limbs and then progressed to all four limbs associated with generalized tiredness. There was no history of associated pain, fever and weakness. The patient had progressive diminution of vision since 2 years and surgery was done for right eye, but vision didn't improve and ended up in blindness. No history of DM, HTN. She is second child of consanguineous marriage. Brother is also dwarf, handicapped (congenital swelling in the lower back leading to paraplegia), no other details were available. No h/o mental retardation in family.

Although there were no antenatal complications, passage of meconium was on fourth day of birth. The patient also had global delay in milestones - head control at one year and walking at two and half years. She had been to school upto 11th standard, could not complete due to loss of vision. She had menarche at the age of fifteen; menstrual cycles were irregular and no menses since last 3 months. She had regular bowel and bladder habits.

On examination: she was short in stature with short neck and depressed nasal bridge. The face was rounded (cushingoid). There was flexion deformity in

Figure 1. **Showing rounded face, short neck and depressed nasal bridge and corneal opacity on the left eye (band keratopathy)**

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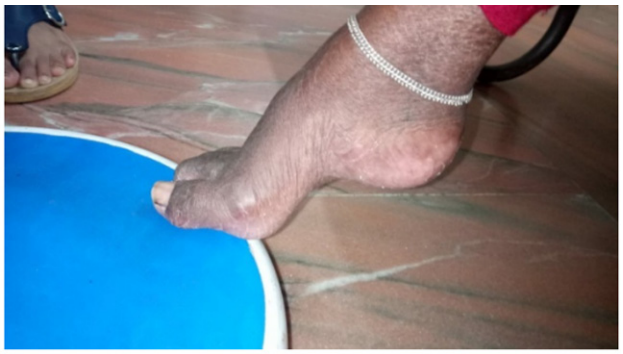

Figure 2. **Showing high arched foot**

bilateral knee joint and high arched foot, flat palm **(figure 2).** Her weight was 32kg and height 102 cm with BMI of 30.76. Chest circumference: 76cm, upper segment: 58cm, lower segment: 44cm, Head circumference: 58cm. she had acanthosis nigricans on skin examination. There was corneal opacity on left eye, cataract and band keratopathy on slit lamp examination **(figure 1).** BP: 100/80 mm of Hg, Pulse: 90/min. per abdomen examination showed distention of abdomen, umbilical hernia was present, no hepatosplenomegaly and no signs of ascites. Central nervous system examination: she was conscious and oriented, higher mental functions normal, no motor deficit, reflexes and sensory system normal. Spine examination showed scoliosis. Cardiovascular and respiratory examination was normal.

Lab investigations showed normal haemogram, liver function tests and serum electrolytes **(figure 3)**. Renal function tests (S.creat: 0.5mg/dl, B.Urea: 16mg/dl) within normal limits. The patient had low serum calcium of 5.7 mg/dl (normal: 8.5- 10.2) and very high value of PTH - 386.7 pg/ml (normal: 10-65). Her serum phosphorous was high - 5.5 mg/dl (normal: 2.5 - 4.5), serum Vit D_3 is 23.37 ng/ml (normal: 20-100) Fasting

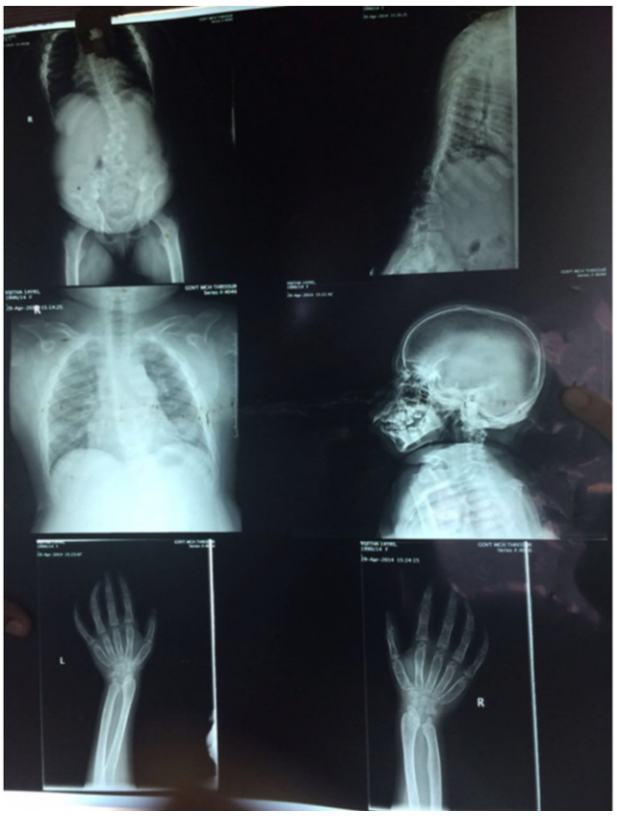

Figure 3. **Skeletal survey showing no evidence of Rickets, Osteomalacia. X-ray of hands showing short 4th and 5th metacarpal bone**

serum cortisol taken at 8 am is 7.98 mcg/dl (normal: 7-28). Spot urine calcium 2.8 mg/dl and spot phosphorus: 28.4mg/dl. X-ray of the hands showed short 4^{th} and 5^{th} metacarpal bone. Skeletal survey showed no evidence of rickets, osteomalacia and mucopolysaccharidosis.

To summarize an eighteen year old female presented with numbness of all four limbs. On examination patient had dwarfism, obesity, moon face, delayed milestones, delayed puberty and umbilical hernia. Lab investigations showed hypocalcemia, high phosphorus, high PTH. The patient was diagnosed as case of Pseudohypoparathyroidism Type Ia. The patient was given calcium replacement (1.5gm/day) active vitD_3 and on review after ten days, her S. Calcium value increased to 8.8 mg/dl. She was very much improved, numbness and tiredness disappeared.

Table 1. Classification of Pseudohypoparathyroidism

Type	Appearance	PTH	Ca	Phos	Response of Urinary cAMP to PTH	Gs alpha Subunit Deficiency	Imprinting Gene defect from
PHP Ia	Skeletal defects (AHO)	High	Low	High	Decreased	Yes	Mother (GNAS1)
PHP Ib	Normal	High	Low	High	Decreased	No	Mother (GNAS1 & STX16)
PHP II	Normal	High	Low	High	Normal	No	-
PPHP	Skeletal defects (AHO)	Normal	Normal	Normal	Normal	Yes	Father

PHP : Pseudohypoparathyroidism, AHO: Albright's hereditary osteodystrophy
PPHP: Pseudopseudohypoparathyroidism,

DISCUSSION

Pseudohypoparathyroidism (PHP) is historically the first hormone resistance syndrome, and it was described for the first time in 1942 by Albright et al.[3] The prevalence of PHP is estimated to be

approximately 0.79 per 100.000.[3] PHP is a group of distinct inherited disorders, characterized by symptoms and signs of hypocalcaemia and high PTH, in association with distinctive skeletal & developmental defects (Albright hereditary osteodystrophy). It is inherited either as Autosomal dominant or X-linked dominant. Inheritance of defective allele from a mother results in Pseudohypoparathyroidsm in offspring and from father results in Pseudopseudohypoparathyroidism in offspring.[1,2]

Hypocalcaemia is due to a deficient response to PTH, which is probably restricted to the proximal renal tubules. There will be tissue resistance to the effects of PTH. Although PTH receptor itself is normal, there is defective post-receptor mechanism due to mutations at $GSAS_1$ locus. Hyperplasia of the parathyroids, a response to hormone resistant hypocalcaemia causes elevation of PTH levels.[1,2]

Although a 24-hour collection is best, random urine calcium measurement can be performed and is expressed in relation to creatinine. A normal reference interval for the urine calcium (mg/dl): urine creatinine (mg/dl) ratio is <0.14. Values exceeding 0.20 are found in patients with hypercalciuria.[6] In our patient the value was 5.6 (2.8/0.5). The normal result for random urine for phosphorus is 68-874 mg/g creatinine for male and 58-846 mg/g creatinine for female for all age groups. It was 56.8 (28.4 /0.5) in our case. These results indicating less excretion of phosphorus and hypercalciuria.

Classification of PHP includes: PHP-Ia, PHP-Ib, PHP-II and PPHP (Pseudopseudohypoparathyroidism). PHP type Ia is the most common pseudohypoparathyroidism with incidence upto 70%. Type Ia PHP is characterized by resistance to PTH and other hormones that stimulate adenyl cycline in their target tissues, such as thyroid stimulating hormone (TSH), gonadotrophins and growth hormone releasing hormone (GHRH)[1,4]. This hormonal resistance leads to hypocalcaemia, hyperphosphatemia, elevated PTH levels, thyroid and gonadal dysfunction. In addition, type Ia PHP is associated with a constellation of peculiar clinical features collectively termed Albright hereditary osteodystrophy (AHO).[1,2,4] These features include short stature, rounded face, brachydactyly (shortness of the fingers and toes), short 4^{th} &5^{th} metacarpals and metatarsals, centripetal obesity, subcutaneous ossifications, and in some cases, mental or developmental delay.[1-5] Patients with type Ia PHP show only about 50% activity of G_s subunit.[4]

Type Ib PHP is characterized by resistance to PTH mainly in the renal tissue and in a few others tissues such as the thyroid, but without features of AHO[4]. Patients with PHP type II have hypocalcaemia, hyperphosphatemia and increased serum PTH, but they lack the physical features associated with AHO[4]

Pseudopseudohypoparathyroidism (PPHP) patients will also have features of Albright's hereditary osteodystrophy but S.calcium & PTH will be normal **(table 1)**[1,2,4]

CONCLUSION

Though rare, possibility of Pseudohypoparathyroidism should be kept in the differential diagnosis while evaluating any patient with hypocalcaemia, hyperphosphatemia and high PTH levels with skeletal & developmental defects. Skeletal survey should be done to rule out evidence of rickets, osteomalacia and mucopolysaccharidosis.

END NOTE

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