Acrophobia in a Young Girl with Parathyroid Hormone Resistance (Pseudohypoparathyroidism)

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ABSTRACT

Pseudohypoparathyroidism (PHP) is an extremely rare group of disorders. It is a spectrum of disorders caused by end organ resistance to parathyroid hormone (PTH) and is represented by impaired signalling that activates cAMP dependent pathways via alpha subunit of G-protein (GSα). It is characterised by hypocalcemia, hyperphosphatemia, raised PTH levels due to insensitivity to biological activity of PTH, and normal renal function tests. We describe a case of 10-year girl who presented with fear of falling down from heights. Her laboratory evaluation and skeletal survey showed evidence of PHP along with features of Albright's hereditary osteodystrophy (AHO) pointing towards the diagnosis of PHP type 1a.

Key Words: *Acrophobia. Parathyroid hormone. Resistance.*

INTRODUCTION

End organ resistance to parathyroid hormone (PTH) gives rise to a group of rare heterogeneous disorders of mineral metabolism characterised by hypocalcemia, hyperphosphatemia and raised PTH levels. Different types of pseudohypoparathyroidism (PHP) have been defined on the basis of their phenotypes, response to PTH stimulation, and testing alpha subunit of G-protein (GSα) activity by *in vitro* assays.[1] PHP type 1 is characterised by a blunt response in urine cAMP to PTH infusion in contrast to PHP type 2. This is probably due to a decreased GSα, that is pivotal in the production of cAMP, the secondary messenger required for downstream signalling. PHP type 1 is further categorised into type 1a, 1b and 1c. A constellation of findings known as Albright hereditary osteodystrophy (AHO) are characteristics of type 1a. Type 1c, being phenotypically similar to type 1a, differs in the coupling of adenyl cyclase to PTH and its receptor.[2,3]

CASE REPORT

A 10-year female resident of Karak, District Kohat, was referred to Armed Forces Institute of Pathology (AFIP), in May 2017 for the evaluation of PTH status. Her parents also complained of her being a slow learner as compared to children of her age and having intellectual disability. She was born through a normal vaginal delivery and had a good cry at birth. Her birth weight was 3.9 kg (>95th percentile). She was breast fed till two years of age. She had a history of delayed milestones; neck holding at 06 months, sitting at 12 months, and walking and talking at two years of age. She had difficulty in learning at school and till date studying in Kindergarten class and could not be promoted to higher levels. She had fear of falling down while walking from the beginning; and over the passage of time, this fear has increased and now she has a lot of difficulty in climbing stairs or heights. There is no history of vomiting, fever, chronic diarrhea, fever, jaundice, diplopia, goiter, seizures, tetany, numbness or any swelling on any body part. Psychological evaluation was not done. There is no significant drug history.

At the time of presentation, she was a well looking, cooperative child, who was fully conscious. She had a blood pressure of 110/70 mmHg in left arm in supine position, pulse rate of 90/min, and a respiratory rate of 25/min. She was afebrile. Cyanosis, icterus, pallor, clubbing, lymphadenopathy, and clubbing were absent. She weighed 23.5 kg (<25th percentile), and had a height of 115.8 cm (<5th percentile) (Figure 1). Her BMI was 17.95 kg/m^2. Systemic examinations of cardio-vascular system, gastrointestinal system, respiratory system, and central nervous system were unremarkable. Skeletal examination revealed short bilateral 3rd, 4th and 5th metacarpals with bilateral short 4th metatarsals (Figures 2 and 3). Family history was insignificant. Her father was 170 cm and mother was 162 cm in height.

On investigating, her blood complete picture, renal and liver function tests were normal. Bone profile showed serum total calcium 1.75 mmol/L (normal range 2.1-2.65), serum inorganic phosphorous 3.2 mmol/L (normal range 1.3-2.25), plasma ionized calcium 1.02 mmol/L (1.16-1.32) and Vitamin D levels were 43 (insufficiency range). Serum albumin was 45 g/L (normal range 35-50). Plasma PTH level was 68.3 pmol/L (normal range 0.8-6). Fertility profile showed serum FSH 5.5 mIU/L (normal

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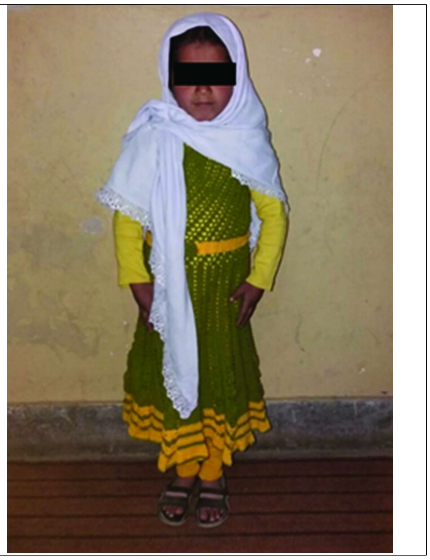

Figure 1: A 10-year old girl with pseudohypoparathyroidism.

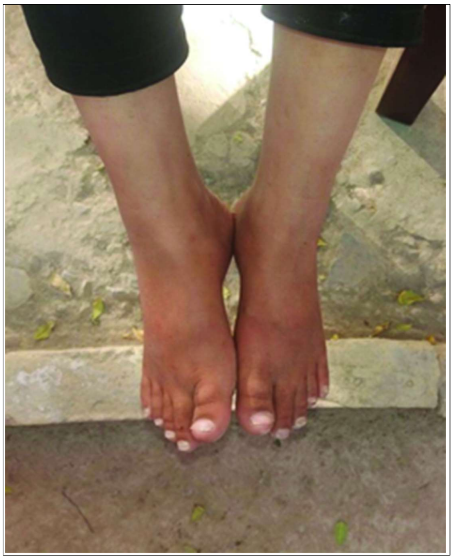

Figure 2: Pseudohypoparathyroidism – brachymetatarsals.

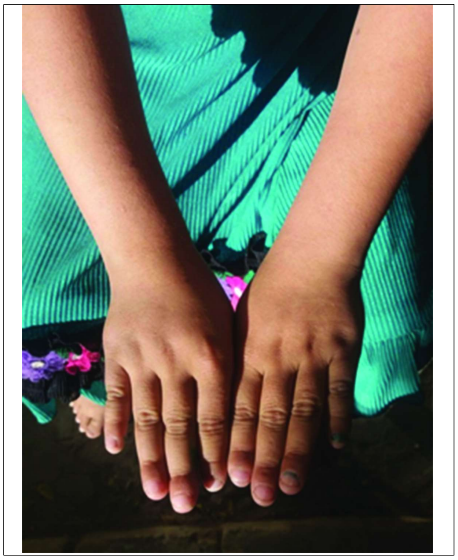

Figure 3: Pseudohypoparathyroidism – brachymetacarpals.

range 1-4), serum LH 0.8 mIU/L (normal range 1-5), serum estradiol <20 pmol/L (normal range 18-220). Thyroid profile revealed raised TSH of 20 mIU/L and (0.7-6.4) with raised T4 of 24 pmol/L (normal range 8.0-21) while a normal T3 of 2.3 nmol/L (normal range 1.1-2.7). Serum creatine kinase was 394 U/L (normal range 20-170). Urine calcium to creatinine ratio was 0.17 and phosphate to creatinine ratio was 3.35.

On radiological investigations, X-ray of hands showed a decrease in bone density and marked cortical thinning and medullary expansion with short 3rd, 4th & 5th metacarpals. CT-scan brain was consistent with the findings of bilateral hyper dense basal ganglia and dense calcification in bilateral tentiform nucleus. Focal area of calcific density in bilateral frontoparietal regions was also seen.

This case had typical clinical and radiological features of AHO (PHP-type-1a). Patient is currently on calcium and vitamin D supplements.

DISCUSSION

G protein, required for the action of PTH, is encoded by the GNAS gene. Both the maternal and paternal alleles of GNAS express the stimulatory GSα, which causes activation of adenyl cyclase, ultimately generating cAMP. PHP type 1a is caused by loss of function mutation of GNAS and maternal transmission of the mutation is necessary for its expression.[4]

The patient had a typical picture of PHP presenting with hypocalcemia, hyperphosphatemia and raised PTH levels. Defect in the signalling pathway leads to the above mentioned features.[5] Sensitivity of the skeleton to PTH calcemic action remains intact because of which bone resorption features were quite evident in this case.[6] The presence of all the peculiar features of AHO like stocky habitus, obesity, short stature, round face, developmental delay, dental hypoplasia, soft tissue calcification, brachymetatarsals, and brachymetacarpals in a patient is very rare.[7] Most of the features of AHO were present in our patient. Growth hormone releasing hormone (GHRH) is another hormone that requires GSα function and also its transcripts are imprinted in the pituitary somatotrophs, which cause the secretion of Growth hormone (GH), thereby affecting the GHRH-dependent somatotrophs stimulation. Thus, mutated GSα also contributes to the short stature of patients presenting with PHP type 1a.[8]

The acrophobic presentation can be explained by the relationship of decreased calcium levels and extinction of conditioned fear learning like acrophobia as explained by Hofmann *et al*.[9] in his study. He proved this by using D-cycloserine which acts as an agonist at the NMDA receptors increasing the intracellular calcium, thus facilitating the extinction of acrophobic symptoms.

TSH and T4 were raised in this patient. These can be explained by the GNAS expression from the maternal allele in the thyroid. This patient also had raised CK as also reported by Isikay *et al*.[10] It may be due to chronic hypocalcemia that causes muscle degeneration.

Raised PTH levels along with hyperphosphatemia, hypocalcemia and normal renal function tests rule out the suspicion of chronic renal failure and hypoparathyroidism, suggesting the presence of PHP. Therefore, it is very important to perform a thorough biochemical evaluation to distinguish PHP from other medical conditions that mimick it.

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