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Endocrinology & Metabolism International Journal

A Case of pseudohypoparathyroidism in a young girl

Abstract

Pseudohypoparathyroidism (PHP) is characterized by hypocalcaemia and hyperphosphatemia due to parathyroid hormone (PTH) resistance. This hormone resistance is usually caused by mutations in the gene guanine nucleotide-binding protein (GNAS) 1 which encodes the alpha (α) stimulating subunit of the stimulatory G protein (Gsa). These mutations contribute to different forms of the PHP: Type 1a, b, c, pseudopseudohypoparathyroidism and type 2. We report here a clinical case of a 12-year-old female with suspected PHP type 1a and we discuss her clinical features, radiographic and laboratory findings along with treatment.

Keywords: Pseudohypoparathyroidism, End-organ resistance, GNAS cluster, Hypocalcaemia

Case Report

Volume 6 Issue 2 - 2018

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Received: December 20, 2015 | **Published:** March 01, 2018

Introduction

Pseudohypoparathyroidism (PHP) is caused by end-organ resistance to parathormone (PTH) and is caused by genetic defects in the imprinted GNAS cluster.[1–3] These gene mutations result in the G-protein inability to activate adenyl cyclase upon binding of PTH to its receptor at the level of the target end organ. Activation of the adenyl cyclase is required for signal transduction that produces the end-organ response to PTH. Failure of signal transduction results in the unresponsiveness of the end organ. The expression of the allele of GNAS 1 gene in humans depends on whether the allele is paternally or maternally inherited and so the disease manifestations also differ depending on which parent passed on the allele.[2]

The type 1a PHP is an autosomal dominant disease and maternal transmission of the mutation (20q13) is required to express type 1a PHP. Type 1a present with a constellation of findings known as Albright's Hereditary Osteodystrophy (AHO) that includes a round facies, short stature, brachydactyly, obesity, subcutaneous calcifications and developmental delay.[4] Resistance of PTH at the level of the renal tubule leads to the following abnormalities: hyperphosphatemia, hypocalcaemia and secondary hyperparathyroidism.[5]

Case report

We report a twelve-year-old female who presented to casualty with inability to walk for 3 years, joint stiffness, and painful spasms of upper and lower limbs for four and half years. She is the 8th child of non-consanguinous parents. Her perinatal history was uneventful. Five years ago she initially presented with bilateral cataract and was treated surgically. Five months later she developed spasms of upper and lower limbs and was thought to have epilepsy. She was put on Phenobarbitone, Carbamazepine and Clonazepam. The spasms persisted and were so severe that she even developed a fracture of the right femur during one of the spasms. She developed progressive weakness of the limbs and generalised joint stiffness over the last three years affecting her mobility

On examination, she had delayed eruption of the permanent teeth after loss of the primary dentition. Her weight and height was 24kg and 123cm respectively both at the 5th centile for her gender and age on the CDC growth chart and her head circumference was 61 cm, above the 97th centile for her age and gender on the CDC chart for head circumferences. She had stiffness of the neck, the temporomandibular joint and of all the upper and lower limb joints. There was shortening of the distal phalanx 3rd to 5th digit as seen by the increased ratio of width of nail to length of nail in Figure 1.

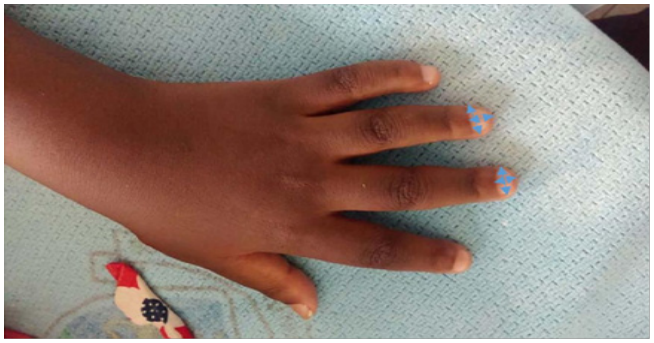

Figure 1 The increased ratio of width of nail to length of nail in figure.

In the musculoskeletal system, the upper limb and lower limbs was kept in flexion with limited range of movements more in the lower limbs as shown in the Figure 2 below.

The tone was increased in all limbs. There was decreased muscle bulk in bilateral all limbs. Child was able to lift the left leg against gravity but could not lift the right leg. The power in all limbs was 3/5. There was hyperreflexia of all the limbs. Bilateral wrists widening and frontal bossing were also noted in the child. Trousseau sign and chovstek signs were positive. Investigations done showed hypocalcaemia, hyperphosphatemia and elevated

PTH. Biochemistry results are summarised in Table 1.

Table 1 Laboratory investigations

Laboratory investigations in chronological order	Magnesium mmol / l (N=0.7-0.86)	Vitamin D 25-OH ng/ml (Deficien-cy < 20)	Alkaline phosphatase U/L (N=42-306)	Calcium level mmol/L (N=2.1-2.5)	Phosphate levels mmol/L (N=1.3-2.3)	Intact Parathyroid hormones pg/mL (N=12-65)
1						250
2				1.88		
3			285	1.91	2.06	
4					2.61	
5	0.69	13	1575			336
6				1.68		
7				1.1.	2.01	
8				0.6	2.42	
9			1499	1,0	2.67	
10			1521	0.9	2.18	

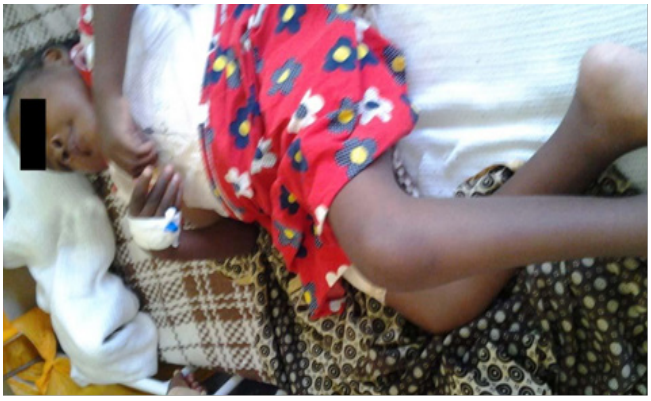

Figure 2 Posture of child.

The serum albumin levels, full blood count, urine analysis, random blood glucose, renal function tests, serum electrolytes and liver function tests were normal.

The X-ray of the wrist as shown in Figure 3 showed cupping and fraying of metaphyseal regions.

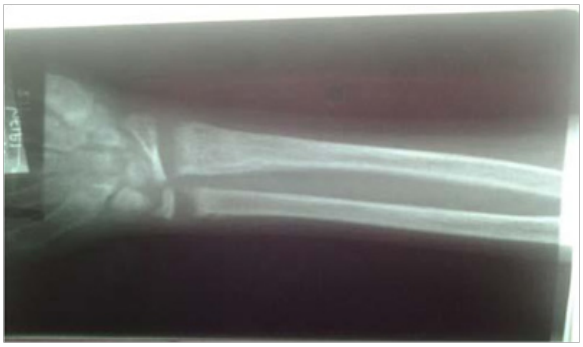

Figure 3 X-ray of the wrist and arm.

The CT-Scan of the cervical spine and the ultrasound abdomen were normal. The CT-Scan of brain showed dense calcifications at the level of bilateral basal ganglia as well as the cortico-medullary junctions of the cerebrum and cerebellum with hyperostosis as seen in Figure 4.

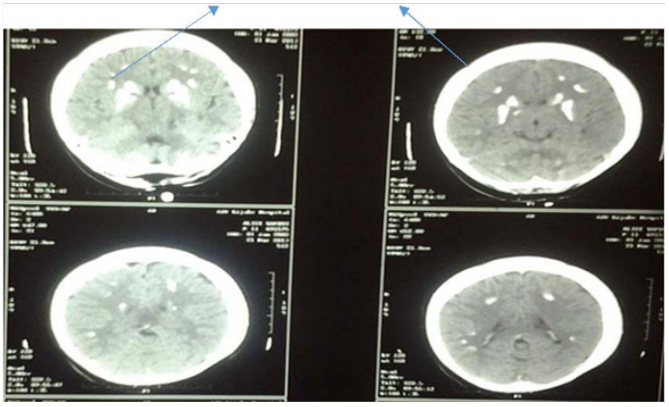

Figure 4 CT-Scan of the brain.

She was managed initially with calcium infusions, aluminium hydroxide and Vitamin D supplements. The calcium levels remained persistently low and parathyroid hormone levels was persistently high and the patient continued to have tetanic convulsions on and off until a serum calcium level of 1.5 mmol/L was achieved. She continued to have joint stiffness leaving her incapacitated. The main challenge in this patient was the delay in making a diagnosis despite seeking care in different institutions and even having her being diagnosed with epilepsy and treated for hypocalcaemia without improvement.

Discussion

Pseudohypoparathyroidism is an uncommon disorder.[6] In 1942, Fuller Albright first used the term, 'pseudohypoparathyroidism' to describe the parathormone resistant hypocalcaemia and hyperphosphatemia. The clinical diagnosis of PHP1a is based on the

presence of PTH resistance (i.e., hypocalcaemia, hyperphosphatemia, and elevated serum PTH) in association with the features of AHO, which includes short stature, obesity, subcutaneous calcification, mental retardation, round facies, and brachydactyly.[5] Paraesthesia, numbness, tetany and convulsions are common presentations of severe hypocalcaemia. Classical clinical signs like Chvostek's and Trousseau's sign are useful pointers for hypocalcaemia.[7] The signs of hypocalcaemia was overlooked in our patient and treated for epilepsy.

Signs of chronic hypocalcaemia includes delayed or absence of permanent tooth eruption, an increase in cavity occurrence and sub-capsular cataracts.[8,9] Hyperostosis was another clinical sign seen in the child. It occurs due to reduced osteoclastic activity, radiologically seen as a dense skeleton and a thickened periosteum due to bone apposition. It affects mainly the long bones, jaw bones and the skull or it can involve the entire skeleton.[10–12] Approximately 50% of patients with PHP exhibit localized calcification of the basal ganglia.[13–15] It was suggested that vascular insufficiency in the extrapyramidal system causes deposition of calcium in the basal ganglia, but there have been no data to definitely support this claim. [16,17]

Although rarely necessary, the demonstration of a blunted response nephrogenous cAMP and phosphate secretion following exogenous PTH administration can contribute to the diagnosis of the type of PHP.[9,18] Assays to measure the concentration of the GS alpha subunit of the adenylate cyclase enzyme and molecular genetic testing such as polymerase chain reaction (PCR)-amplified genomic DNA helps to detect mutations in the GNAS1 gene. This gene codifies the subunit α of protein Gs, mapped in chromosome 20q13.2- 20q13.3.[1,3,9,19,20]

PHP is classified into the following types: Type 1a, b, c, pseudopseudohypopara- thyroidism and type 2. The types and features of PHP is summarised in Table 2.

Table 2 Classification and clinical features of pseudohypoparathyroidism subtypes

Type	↓ Calcium ↑ Inorganic Phosphate	Urinary cAMP response to PTH	PTH	Gsα subunit Deficiency	AHO	Hormonal resistance	Cause
PHP -1a	yes	↓	↑	yes	yes	Multiple	Gs mutation
PHP -1b	yes	↓	↑	no	no	PTH	Non-methylation of promoter 1A
PHP -1c	yes	↓	↑	no	yes	Multiple	unknown
PHP -2	yes	normal	↑	no	no	PTH	Acquired defect?
PPHP	no	normal	normal	yes	yes	None	Genomic imprinting

It was not possible to do molecular genetic testing such as polymerase chain reaction (PCR)-amplified genomic DNA which would have helped to detect mutations in the GNAS1 gene due to cost implications. The presence of hypocalcaemia, hyperphosphatemia and high PTH levels with signs of Albright's hereditary osteodystrophy, pointed to the diagnosis of PHP of type 1a type.

We treated this patient with oral Calcium and an active form of a Vitamin D analogue and noted a partial clinical and laboratory response. She remains on close follow up, with a step up of doses and is on serial clinical and laboratory surveillance.

Acknowledgements

We thank Dr. Peninah Musyoka and Dr. Lucy Mungai for their contribution in the workup and treatment of our patient.

Conflict of interest

None.

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