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Seizure Beyond Brain: A Case Report on Pseudohypoparathyroidism

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Abstract:

Pseudohypoparathyroidism (PHP) represents a group of disorders due to end organ resistance to the actions of parathyroid hormone (PTH) and abnormalities in the PTH signaling pathway. PHP is characterized by hypocalcemia and hyperphosphatemia with variable expression of clinical phenotype. The constellation of these clinical features together is termed as Albright hereditary osteodystrophy (AHO). Molecular genetics is the gold standard for confirmation and categorization of PHP into the different subtypes. Despite recent advances in molecular diagnostics, clinical approach appears to be more practical in resource limited setting. Here, we discuss about clinical features, radiographic abnormalities, laboratory findings and treatment of an 8-year-old-girl with pseudohypoparathyroidism.

Keywords: Pseudohypoparathyroidism, Albright hereditary osteodystrophy, hypocalcemia, hyperphosphatemia

Introduction

The term pseudohypoparathyroidism (PHP) refers to a set of diseases caused by anomalies in the PTH signaling pathway and end organ resistance to the effects of parathyroid hormone

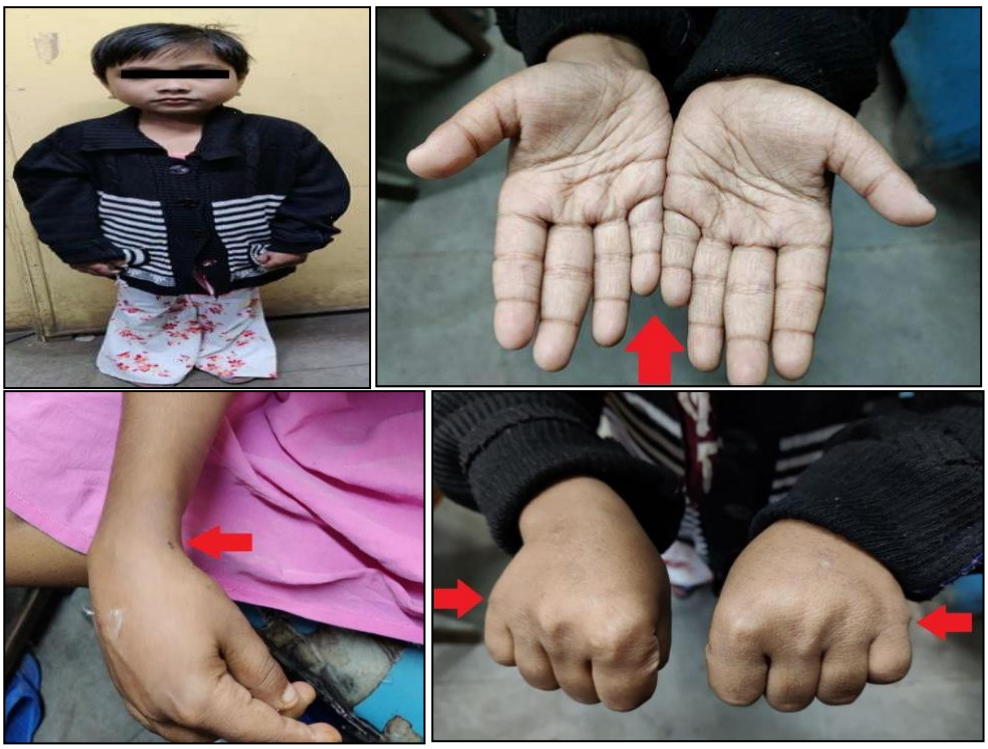
(PTH). Albright hereditary osteodystrophy (AHO), a constellation of these physical abnormalities, is the name given to PHP, which is characterized by hypocalcemia, hyperphosphatemia, and high PTH levels. Prevalence is 0.3 to 1.1 cases per 100,000 population worldwide.[1]

Pseudopseudohypoparathyroidism (PPHP), progressive osseous heteroplasia (POH), osteoma cutis, and acrodysostosis are other conditions linked to PTH resistance and PTH signaling pathway dysfunction. [2] The PTH/PTHrP (parathyroid hormone related-protein) signaling pathway is altered genetically and/or epigenetically in PHP. The primary genetic abnormality is brought on by inactivating mutations in the GNAS gene, which is responsible for a number of gene products, including transcripts that encode the subunit of the stimulatory guanine nucleotide-binding protein (G protein).[3] PHP is classified into several distinct entities (type Ia, Ib, Ic, type II), according to the molecular causes and clinical features of the patients.[4–6] PHP and the features of AHO were initially outlined by Fuller Albright and associates in 1942.[8]

Case Report:

An 8-year-old girl patient was admitted to our Pediatric department with history of 3 episodes of generalized tonic clonic seizure, each episode lasting for 5 minutes. She was born out of first degree consanguineous marriage with uneventful postnatal period. She had never undergone any surgical procedure and was not under any medication. Her height was 117 cm ( ) and weight was 20 kg ( ). Neurological evaluation revealed no abnormalities.

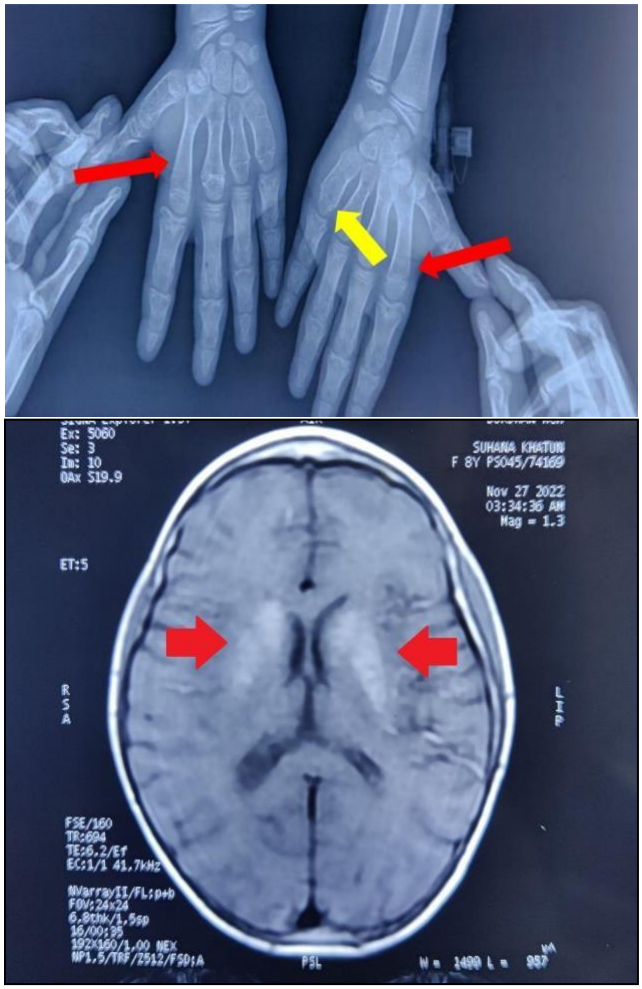
Subsequently, she developed two episodes of carpo-pedal spasms on the second day (Figure 4). She had similar episodes 3 years ago with tingling and numbness like sensation in all four limbs. There was no episode of convulsion during the hospital stay. Physical examinations revealed that, she had round facies and stocky built (Figure 1). She had short 4th and 5th digits (brachydactyly) and squaring of palmer surfaces of both hands (Figure 2). There was absence



of knuckling over dorsum of 4th and 5th digits of both hands in fist state, Archibald's sign (knuckle knuckle dimple dimple sign) (Figure 3).

Figures 1-4: Physical examination; Clockwise from the top left: Figure 1 - round facies and stocky built, Figure 2 - brachydactyly in 4th and 5th digits and squaring of palmer surfaces, Figure 3 - absence of knuckling over dorsum of 4th and 5th digits, Figure 4 - carpo-pedal spasm

Skiagram of her hands showed long 2nd metacarpal and gradual shortening of metacarpals in both hands (Figure 5). This was indicative of Albright hereditary osteodystrophy. MRI brain showed bilaterally symmetrical altered intensity of both sides of dentate nucleus, mid brain, basal ganglia and peri-ventricular area, which suggests calcifications (Figure 6). Renal ultrasound findings were within normal limits.



Figures 5-6: Radiological examination; From Top to bottom: Figure 5 - X-ray shows long 2nd metacarpals (red arrow) and gradual shortening of metacarpals (yellow arrow), Figure 6 – MRI brain shows bilaterally symmetrical altered intensity of both sides of dentate nucleus, mid brain, basal ganglia and peri-ventricular area

Laboratory reports are shown in Table 1 which represents hypocalcaemia, hyperphosphatemia, and high PTH levels. Teriparatide challenge test for urine CAMP (Chase – Aurbach test) and urine phosphate (Ellsworth – Howard test) could not be done due to lack of facilities.

PARAMETERS	VALUES	

Serum Calcium	6.2 mg/dl	
Serum Phosphate	15.3 mg/dl	
Serum Magnesium	1.6 mg/dl	
Serum Urea	20 mg/dl	
Serum Creatinine	0.7 mg/dl	
Serum Vitamin D3	37.78 ng/ml	
Urine Calcium	0.14 mg/dl	
Uric acid	3.4 mg/dl	
Creatine kinase	55 U/L	
Parathyroid hormone	230.60 pg/ml	
Growth hormone	0.085 ng/ml	
FSH	3.45 mIU/ml	
LH	0.27 mIU/ml	
TSH	10.53 mIU/ml	

Table 1. Laboratory reports

Genetic analysis showed pathogenic, heterozygous deletion variant at exon 7 of GNAS gene, confirming the diagnosis of Pseudohypoparathyroidism Type Ia.

After conservative management, the girl was discharged with syrup calcium (250/5) and syrup valproate (200/5) at the dose of 20 mg/kg/day.

Discussion:

Understanding the pathophysiologic basis of PHP has improved as a result of recent advancements in genetic testing. Despite the limited accessibility of genetic testing, a taxonomy of the suspicious clinical traits that may help identify cases has just been published. The GNAS gene, which codes for the alpha subunit of G-protein coupled receptors, is found on the long arm of chromosome 20. This gene's transcript is controlled by an alternate splicing mechanism that enables the expression of three distinct proteins: Gs-alpha, extra-large (XL) s, and the chromogranin-like protein, which stands in for Gs-alpha subunit in neuroendocrine regions. All of the Gs-alpha protein seen in neuroendocrine organs such the hypophysis, thyroid gland, ovaries, and testicles as well as renal tubules is encoded in the maternal allele due to methylation of exon 1 from the paternal allele. Maternal inheritance of such a mutation leads to PHP-Ia, i.e., AHO plus hormone resistance, while paternal inheritance of the same

mutation leads to PPHP, i.e., AHO only. This imprinted mode of inheritance for hormone resistance can be explained by the predominantly maternal expression of Gs-alpha in certain tissues, including renal proximal tubules. Depending on whether the mother or the father inherits the mutation, the clinical signs and symptoms of this autosomal dominant condition will vary. Except for the endocrine tissues, which will continue to express the typical levels of this protein from the maternal allele. The important clinical features in our case are hypocalcaemia, hyperphosphatemia, elevated PTH levels and stocky built, short stature with brachydactyly in 4th and 5th digits and absence of dimpling over 4th & 5th digit on dorsum of hand while making fist, Archibald's sign (knuckle knuckle dimple dimple sign) are typical findings of AHO. Then finally on MRI we got basal ganglia calcification. All these findings supported our diagnosis of pseudohypoparathyroidism in this case

We treated this patient with intravenous calcium gluconate to correct her low serum calcium level. She was discharge with oral calcium and Syrup valproate. She remains on close follow up, with a step up of doses and is on serial clinical and laboratory surveillance.

Conclusion:

Pseudohypoparathyroidism type 1A is an autosomal dominant disorder, caused by deletion of maternal copy of GNAS gene. Some cases are termed as Albright's Hereditary Osteodystrophy depending on the clinical features. Though pseudohypoparathyroidism is a rare disease entity, it should be considered as a differential in cases of repeated convulsions with refractory hypocalcemia. Meticulous clinical examination is the key for clinching the diagnosis.

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