TPM Vol. 32, No. S1, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

AN INFANT WITH SEIZURES, OBESITY, AND ELECTROLYTE IMBALANCE: REVEALING PSEUDOHYPOPARATHYROIDISM

SHALINI PRIYA NANDAGOPAL[1], ASHWINI A[2], KOUSALYA KUMAR[3], JOSHUA RAJAN X[4], SYED MOHAMMED H[5], DR. MOHAN VALIATHAN[6]

[1,2,3,4,5] PAEDIATRICS, SAVEETHA MEDICAL COLLEGE AND HOSPITAL, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES, SAVEETHA UNIVERSITY, CHENNAI, INDIA
[6]PROFESSOR, DEPARTMENT OF PERIODONTOLOGY, SREE BALAJI DENTAL COLLEGE & HOSPITAL, CHENNAI, INDIA
CORRESPONDING AUTHOR: SYED MOHAMMED H

Abstract

Children having pseudohypoparathyroidism (PHP), an inherited disorder defined by end-organ resistance to parathyroid hormone (PTH), could suffer from growth retardation, seizures, tetany, obesity, and electrolyte imbalance. We report the case of an obese infant presenting with seizures, cardiac failure, and respiratory distress. Laboratory investigations revealed microcytic hypochromic anemia, hypothyroidism, hypocalcemia, hyperphosphatemia, vitamin D insufficiency, and elevated PTH levels. The infant was shifted to intensive care for respiratory distress and congestive cardiac failure. Management included non-invasive ventilation, blood transfusion, and calcium and magnesium supplementation, with serial monitoring of electrolytes and PTH levels. Whole genome sequencing confirmed a GNAS-related genetic mutation, establishing the diagnosis of pseudohypoparathyroidism. This case demonstrates the challenges in detecting PHP in children in light of its peculiar and dynamic clinical manifestation.

Keywords: gnas, electrolyte imbalance, growth retardation, obesity, seizures, pseudohypoparathyroidism

INTRODUCTION

Target organ resistance or inability to respond to PTH, as well as increased plasma parathyroid hormone (PTH) levels instead of the low levels usually observed in hypoparathyroid conditions, are the hallmarks of pseudohypoparathyroidism (PHP), an atypical inheritable disease. GNAS gene mutations affect the G stimulatory protein's capacity to activate adenyl cyclase when PTH binds to its receptor, leading to end-organ resistance to PTH [1]. Mantovani et al. have described several subtypes of PHP-1A and 1B. Depending on the particular mutation, people with PHP type 1A may also have resistance to other hormones, which can result in disorders including primary hypothyroidism, hypogonadism, and short stature. PHP type 1A is characterised by loss-of-function mutations in genes such as GNAS, PRKAR1A, PDE4D, or PDE3A. Although there have been isolated reports of TSH resistance, PHP type 1B typically exhibits no other endocrine problems [2]. PHP type 2 is limited to resistance to PTH. Fuller Albright et colleagues. initially identified PHP in 1942 in patients who showed resistance to PTH treatment and decreased excretion of phosphate and cyclic AMP in the urine [3]. Albright's hereditary osteodystrophy (AHO) is phenotypically expressed anytime the mutant GNAS gene is inherited; maternal inheritance results in both AHO and multi-hormone resistance, while paternal inheritance produces AHO characteristics without PTH resistance [4].

Case Presentation

An 11-month-old male child, first born, to a non-consanguineous marriage, came with complaints of fever for one day which was high grade and intermittent. Mother also gave history of two episodes of seizures lasting for less than 10 seconds. After an episode of excessive crying, mother also noted bluish discoloration of lips during the 2nd episode. No history of vomiting, loose stools, difficulty in urination, breathing difficulty or altered sensorium was noted. Child was tolerating feeds well. Child had no prior history of consultation for any other illness. Antenatally, mother had history of anaemia treated with eight doses of iron sucrose. Baby was born at term by caesarean section with birthweight of 3.7 kilograms. Postnatal period was uneventful. Child was exclusively breast fed. The child exhibited significant developmental delay, with the motor component being most affected. On examination, the child was febrile with tachycardia and tachypnoea. Anthropometric measurements revealed

weight for age and weight for length more than 97th percentile. Child had severe pallor, laryngeal stridor, round face, premature fusion of cranial sutures and no dentition was noted, as seen in Figure *1*. Systemic examination revealed normal heart sounds with systolic murmur over mitral region. Soft non tender Hepatomegaly was seen. The child was diagnosed with congestive cardiac failure and started on non-invasive ventilation. Child was initiated on blood transfusion.

FIGURE 1: Profile of a 11-month-old infant with pseudohypoparathyroidism at admission

An obese child with round face is noted in the image above

Laboratory tests revealed severe anemia, elevated alkaline phosphatase (ALP), hypocalcemia, hypomagnesemia, and hyperphosphatemia. Further evaluation revealed elevated parathyroid hormone (PTH) and insufficient vitamin D levels as seen in Table *1*. A peripheral smear showed microcytic hypochromic anemia with anisopoikilocytosis, while iron studies confirmed iron deficiency anemia. High- Performance Liquid Chromatography was found to be normal. Hormonal evaluation revealed elevated thyroid-stimulating hormone (TSH) levels, suggestive of hypothyroidism. Chest X ray indicated apparent cardiomegaly & hepatomegaly as seen in Figure *2*. X-ray of left hand revealed short, broad metacarpals, especially the 1st, suggesting brachydactyly, bullet-shaped phalanges, and fraying of the distal metaphysis as seen in Figure *3*. CT Brain revealed skull vault thickening with copper beaten skull appearance

Investigations	Value	Reference range	Interpretation
Hemoglobin (g/dl)	5.7	13-17	Anemia
Red blood cells (million/cu.mm)	4.18	4.5-5.5	
Packed cell volume (%)	21.7	40-50	
Total leukocyte count (cells/cu.mm)	12510	4000-10000	
Serum calcium (mg/dl)	4.3	9-11	Hypocalcemia
Serum magnesium (mg/dl)	1.5	1.6-2.3	Hypomagnesemia
Serum phosphorus (mg/dl)	6.2	3-5	Hyperphosphatemia
Alkaline phosphatase (IU/L)	903	38-126	Elevated
Vitamin D (ng/ml)	21.3	30-100	Insufficient
Parathormone (pg/ml)	542.2	10-65	Elevated
Free triiodothyronine (pg/ml)	4.03	2.77-5.27	Hypothyroidism
Free thyroxine (ng/dl)	1.03	0.78-2.19	
Thyroid stimulating hormone (mIU/ml)	8.856	0.5-4.5	
Serum iron (mcg/dl)	18	37-170	Low
Serum ferritin (ng/ml)	6.27	17.9-464	Low
Total iron binding capacity (mcg/dl)	467	261-462	High

TABLE 1: Laboratory investigations of the Child

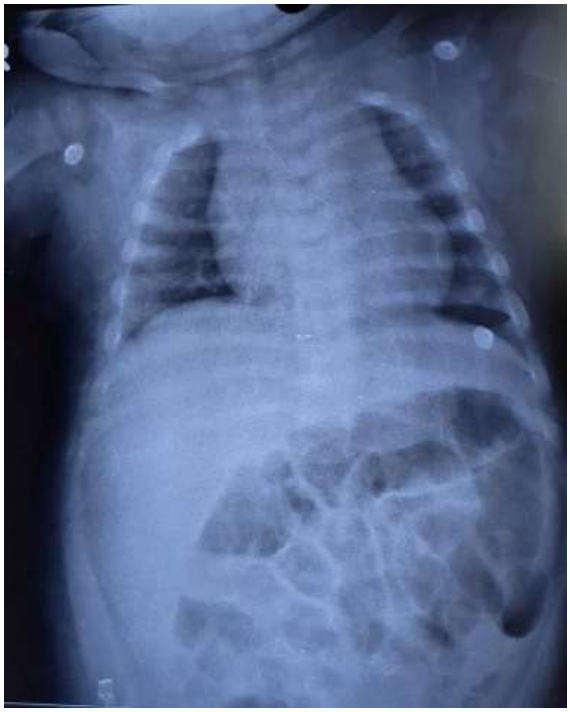


FIGURE 2: Xray of chest and abdomen

Cardiomegaly and hepatomegaly are noted in the x-ray above

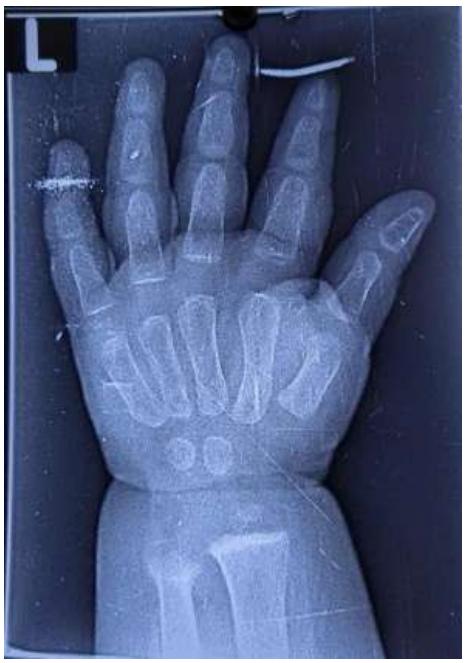


FIGURE 3: X-ray of the left hand and wrist

The above x-ray shows short, broad metacarpals-brachydactyly, bullet-shaped phalanges, and fraying of the distal metaphysis.

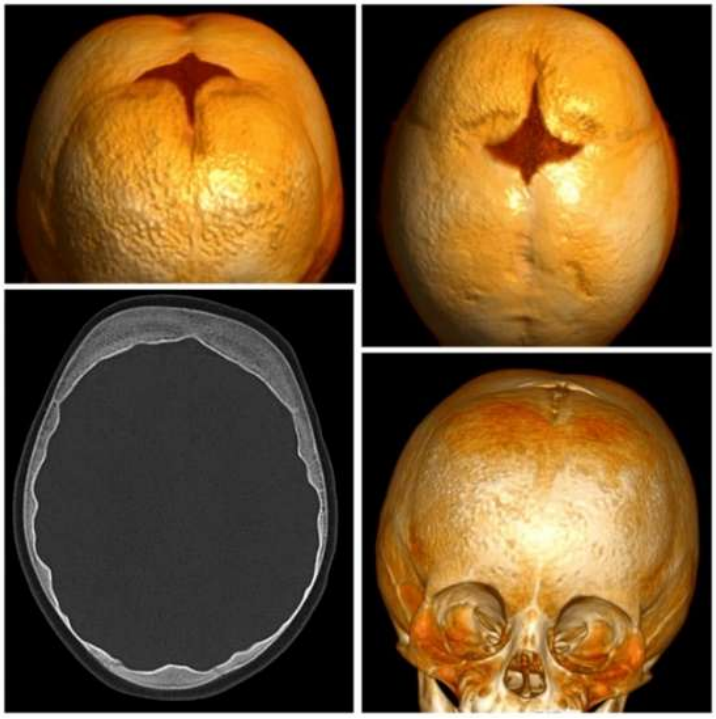


FIGURE 4: CT brain and skull of the child

The above CT scan shows skull vault thickening with diffuse hyperostosis, copper beaten skull appearance and craniosynostosis of coronal suture

We have a child with obesity, developmental delay, seizures, severe iron deficiency anemia with congestive cardiac failure, laryngeal stridor, craniosynostosis, hypocalcemia, hypomagnesemia, hyperphosphatemia, elevated PTH, vitamin D insufficiency & hypothyroidism. The child was diagnosed with pseudohypoparathyroidism and started on intravenous calcium correction, oral supplementation of calcitriol, calcium carbonate and magnesium. Child had multiple episodes of apnea while feeding. Child had bluish discoloration of limbs and shallow respiratory efforts. Child was managed with non-invasive ventilation support. Whole exome sequencing was done. The detected variant of GNAS gene is associated with pseudohypoparathyroidism heterozygous likely pathogenic variant in GNAS gene. Exon 12: c.1006c>t, p. Arg336trp, autosomal dominant inheritance as seen in Table *2*.

Test results and interpretation						
Heterozygous likely pathogenic variant detected: Clinical correlation recommend						
Summary of Variants						
Gene and transcript	Exon/intron number	Variant nomenclature [variant depth/total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
GNAS (NM_000516.7)	Exon 12	c.1006C>T, p. Arg336Trp [98x/181x]	Heterozygous	Likely pathogenic	GNAS associated pseudohypoparathyroidism	Autosomal dominant

TABLE 2: Whole exome sequencing report of the child

DISCUSSION

Symptoms such as numbness or tingling, painful muscular spasms, seizures, low blood pressure, emotional instability, and developmental delay can appear in children with pseudohypoparathyroidism (PHP). Levine et al. have noted common clinical characteristics, including brachydactyly, low stature, obesity, round face, short neck, subcutaneous ossifications, hazy vision, and the "knuckle, knuckle, dimple, knuckle" sign, which indicates

shortened metatarsals [5]. Numerous signs of AHO are present in this 11-month-old kid, and further symptoms are continuously being noted. AHO characteristics are shared by pseudo-pseudohypoparathyroidism and PHP type 1A. According to Fitch et al., despite their low stature, almost one-third of children with AHO weigh more than the 90th percentile for their age, indicating that they frequently suffer from obesity [6].

Hejlesen et al. found that children with PHP also had coarse, brittle hair and nails, as well as dental problems like teeth that mature later and enamel that is weaker [7]. Under the category of inactivating PTH/PTHrp Signalling Disorders (iPPSD), which includes types 1A and 1B, craniosynostosis has been observed in pseudohypoparathyroidism [8].
In line with its varied clinical manifestations, similar case reports have found pseudohypoparathyroidism at different ages and phases of life. A nine-year-old child who was treated for hypercalcemic convulsions and who did not exhibit any signs of AHO but had a round face and obesity was the subject of a case report by Morgado et al. [9]. The periods of hypocalcaemia happened during puberty, most likely as a result of the increasing calcium requirements at that time.

According to a case study by Su Kyeong et al., a newborn with congenital hypothyroidism was later identified with osteoma cutis. Although the youngster did not show any symptoms of obesity, they did have characteristics of AHO [10].The child in this case report complained of seizures, which made it necessary to determine the underlying cause. The infant was diagnosed with severe anaemia and hypocalcaemia after experiencing two episodes of febrile seizures. In this instance, severe iron deficiency anaemia, a fever over 100°F, male gender, and a seizure lasting less than five minutes were identified as key risk factors for febrile seizures [11].

In order to minimise PTH levels and prevent bone resorption, PHP management focusses on controlling calcium and phosphorus levels while preventing hypercalciuria. When given the right amount of calcium and vitamin D, children with moderate PHP typically have normal lives. Regular monitoring, including yearly evaluations of blood calcium, phosphorus, PTH, vitamin D, and urine calcium levels, was advised by Donghi et al. [12].

Obesity is a major risk factor for Obstructive Sleep Apnea (OSA) in children, leading to airway obstruction during sleep. OSA is characterized by apnea (complete pauses) and hypopnea (shallow breathing), measured by the Apnea-Hypopnea Index (AHI) during polysomnography. Higher AHI values indicate more severe OSA, which can cause cardiovascular issues, cognitive impairment, and metabolic disturbances. [14] Obesity in children is a major risk factor for type 2 diabetes, as excess body fat leads to insulin resistance and impaired glucose metabolism. This results in elevated blood sugar levels, increasing the risk of complications like cardiovascular disease and metabolic syndrome [15].

In addition to regularly monitoring growth and screening for endocrinopathies, periodic ECGs are advised to monitor the QT interval and evaluate the risk of arrhythmias. Significant morbidity and mortality can result from severe cases, which are characterised by obesity, sleep apnoea, and developmental delay. Effective follow-up and management require a multidisciplinary approach.

CONCLUSIONS

This case report of an infant with PHP who presented with seizures, heart failure, and developmental delay highlights the importance of taking PHP into account when diagnosing hypocalcaemia in infants and young children. In order to avoid difficulties and enhance outcomes for impacted children, this paper highlights the need of increasing awareness among medical professionals, the necessity of a high degree of clinical suspicion, early diagnosis, and timely intervention.

REFERENCES

1. Mantovani G, Bondioni S, Linglart A, et al.: Genetic analysis and evaluation of resistance to thyrotropin and growth hormone-releasing hormone in pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 2007, 92:3738-42. 10.1210/jc.2007-0869

2. Joshi R, Kapdi M: Pseudohypoparathyroidism type 1b with hypothyroidism. Indian Pediatr. 2012, 49:667-8. 10.1007/s13312-012-0123-4

3. Germain-Lee EL: Management of pseudohypoparathyroidism. Curr Opin Pediatr. 2019, 31:537-49. 10.1097/MOP.0000000000000783

4. Mantovani G, Maghnie M, Weber G, et al.: Growth hormone-releasing hormone resistance in pseudohypoparathyroidism type ia: new evidence for imprinting of the Gs alpha gene. J Clin Endocrinol Metab. 2003, 88:4070-4. 10.1210/jc.2002-022028

5. Levine MA: Clinical spectrum and pathogenesis of pseudohypoparathyroidism. Rev Endocr Metab Disord. 2000, 1:265-74. 10.1023/a:1026510200264

6. Fitch N: Albright's hereditary osteodystrophy: a review. Am J Med Genet. 1982, 11:11-29. 10.1002/ajmg.1320110104

7. Hejlesen J, Underbjerg L, Gjørup H, Sikjaer T, Rejnmark L, Haubek D: Dental anomalies and orthodontic characteristics in patients with pseudohypoparathyroidism. BMC Oral Health. 2019, 20:2. 10.1186/s12903-019-0978-z.

8. Di Rocco F, Rothenbuhler A, Cormier Daire V, et al.: Craniosynostosis and metabolic bone disorder. A review. Neurochirurgie. 2019, 65:258-263. 10.1016/j.neuchi.2019.09.008

9. Morgado J, Dias P, Sampaio M de L, Sousa AB: A sporadic case of pseudohypoparathyroidism type Ib. Rev Port Endocrinol Diabetes E Metab. 2016, 11:212-4. 10.1016/j.rpedm.2016.02.009

10. Hwang SK, Shim YJ, Oh SH, Jang KM: Early Diagnosis of Pseudohypoparathyroidism before the Development of Hypocalcemia in a Young Infant. Children (Basel). 2022, 9:723. 10.3390/children9050723

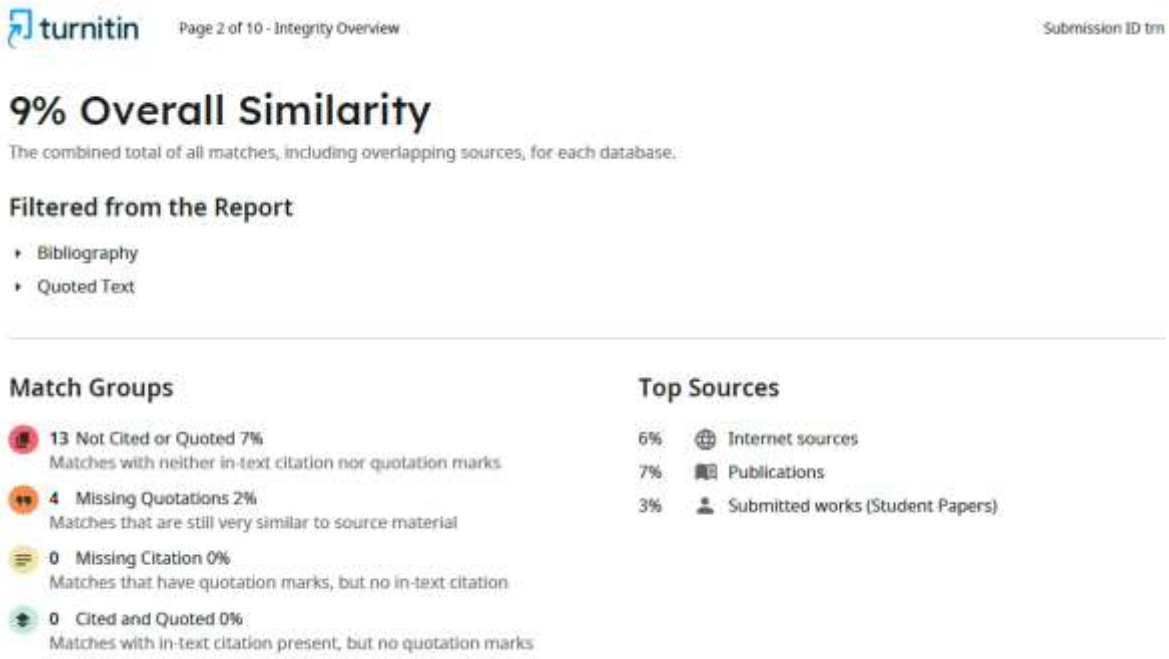
11. Parellangi, Devanand G C, Sakshi U B, Harsha V, Radha K, S Prashanth: To study the risk factors for recurrence of febrile seizures in children in southern India. J PHARM NEGATIVE RESULTS. 2023, 14:87-92. 10.47750/pnr.2023.14.01.014

12. Donghi V, Mora S, Zamproni I, Chiumello G, Weber G: Pseudohypoparathyroidism, an often delayed diagnosis: a case series. Cases J. 2009, 2:6734. 10.1186/1757-1626-2-6734

13. Aldabbas MM, Tanwar T, Ghrouz A, et al. A polysomnographic study of sleep disruptions in individuals with chronic neck pain. J Sleep Res. 2022;31(5)

14. Yelkur P, Manivel R, Chandrasekhar V, Mohammed S, Narayan K. Comparative study of myofascial exercise and the voluntary breathing technique on the apnea-hypopnea index among adolescents. *Cureus*. 2024 Jul 13;16(7):e64483. doi: 10.7759/cureus.64483. PMID: 39139327; PMCID: PMC11319656.

15. Rajendran S, Mishra S, Madhavanpillai M, et al. Association of hemoglobin glycation index with cardiovascular risk factors in non-diabetic adults: a cross-sectional study. *Diabetes Metab Syndr*. 2022;16(9).


turnitin Page 2 of 10 - Integrity Overview Submission ID trn

9% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

Filtered from the Report

- Bibliography
- Quoted Text

Match Groups

13 Not Cited or Quoted 7%
Matches with neither in-text citation nor quotation marks

4 Missing Quotations 2%
Matches that are still very similar to source material

0 Missing Citation 0%
Matches that have quotation marks, but no in-text citation

0 Cited and Quoted 0%
Matches with in-text citation present, but no quotation marks

Top Sources

6% Internet sources
7% Publications
3% Submitted works (Student Papers)