

# Pseudohypoparathyroidism as a Cause of Refractory Seizures

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## Abstract

Pseudohypoparathyroidism is a genetic disorder that is similar to hypoparathyroidism, but which results from the body's lack of response to parathyroid hormone rather than its decreased production. Serum level of immunoreactive Parathormone are elevated instead. We report a four month old infant in status epilepticus associated with hypocalcemia, hyperphosphatemia and raised parathyroid hormone level. Hypocalcemia was resistant to calcium therapy initially but responded to vitamin D analogue therapy leading to diagnosis of Pseudohypoparathyroidism.

**Key words:** Hypocalcemia, Seizures, Pseudohypoparathyroidism

## Introduction

Pseudohypoparathyroidism (PHP) is a term used to describe several related disorders characterised by end organ unresponsiveness to parathormone, due to receptor or post receptor defects<sup>1</sup>. Serum level of immunoreactive PTH are elevated even when patient is hypocalcaemia or normocalcemic<sup>2</sup>. PHP is listed as a rare disease by Office of Rare Disease (ORD) of National Institute of Health (NIH). This means that PHP or a subtype of PHP affects less than 200,000 people in US population<sup>3</sup>. The characteristic biochemical derangements include hypocalcemia, hyperphosphatemia and high serum parathormone levels<sup>1</sup>. Patients diagnosed with type1A PHP have short, stocky build, brachydactyly with dimpling of dorsum of hands. Other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of calvaria are also found. Patients with type1B and type 2 PHP are phenotypically normal<sup>2</sup>.

## The Case

A four month old male child weighing 4 kg was brought to paediatric emergency with status epilepticus. Seizures were not controlled with IV loading Phenytoin, Phenobarbitone. Midazolam infusion was started and investigations sent showed low serum calcium levels (6.8mg/dl). IV Calcium gluconate was infused slowly and seizures aborted within five minutes. History of recurrent seizures was present since 20<sup>th</sup> day of life. They were secondary generalized seizures which stopped spontaneously after some time as said by mother. Child was on phenobarbitone since two months

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of age and was admitted at 2.5 months of age with status epilepticus in a private hospital. Child was first in birth order, born by caesarean section at term with birth weight of 2.5 kg. Immediate perinatal period was uneventful with no history of birth asphyxia. Developmental milestones were slightly delayed. Sepsis workup and CSF examination were normal. Thyroid profile was also normal. Serum calcium level were repeated and found to be low (total calcium 7.3 mg/dl, ionic calcium fraction 3.3 mg/dl) despite continuous IV maintenance calcium infusion. Serum magnesium levels were normal. Later PTH level by radioimmunoassay was found to be 120 pg/ml (normal:10-70 pg/ml). Serum vitamin D2 levels were also sent but they were normal and serum phosphorus levels were elevated. Diagnosis of PHP was made and child was put on oral calcitriol (0.25 µg/day)

along with oral calcium supplements. Child remained seizure free during subsequent stay in hospital and also on follow up after two months. Antiepileptics were tapered and stopped. Child is on follow up had normal serum calcium and phosphorus levels.

Child didn't have any physical stigmata on examination which are found usually in type 1A PHP like short, stocky build, brachydactyly with dimpling of dorsum of hands. Other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of calvaria were also not found.

## Discussion

PHP is a genetic disorder which manifests with parathyroid hormone (PTH) resistant hypocalcemia and hyperphosphatemia. In PHP, parathyroid glands are normal or hyperplastic histologically and neither endogenous nor administered PTH raises serum calcium level or lowers the level of phosphorus. The genetic defect in hormonal receptor adenylate cyclase system are classified into various types depending on phenotypic and biochemical findings<sup>2</sup>.

There are two main types: Type-1 and Type-2. Type-1 is characterised by low or absent urinary phosphates and cAMP production in response to exogenously infused PTH but Type-2 responds with normal increase in urinary cAMP but shows absent or subnormal phosphaturic response<sup>4</sup>. Type-1 is further subdivided into 1A and 1B. Type-1A patients have genetic defect of  $\alpha$  subunit of stimulatory guanine nucleotide binding protein. This coupling factor is required for PTH bound to cell surface receptors to activate cAMP. Heterogeneous mutations of Gs $\alpha$  gene have been documented; gene is located on 20q13.2. Deficiency of the Gs $\alpha$  subunit is a generalized cellular defect and account for association of other endocrinal disorders with Type-1A PHP<sup>2</sup>. Type-1B patients have normal phenotypes and normal G protein activity. There is tissue specific resistance to PTH but not to other hormones<sup>2</sup>. Type-2 patients are phenotypically normal but hypocalcemia is present. Defect appears to be distal of cAMP because it is normally activated, but cell is unable to respond to the signal<sup>2</sup>.

Our case presented in status epilepticus due to hypocalcemia which was resistant to correction with IV calcium. Serum phosphate levels were raised but serum magnesium levels and vitamin D levels were normal in presence of raised PTH found in our case which precludes hypoparathyroidism due to low magnesium levels and hypoparathyroidism due to overt vitamin D deficiency hence confirming diagnosis of PHP. But

our case did not have any morphological features like obesity, short metacarpals or exostoses which are found in Type-1A or Albright Hereditary Osteodystrophy.

Main goal of therapy is to maintain normal calcium levels and to suppress PTH levels to normal with use of 1  $\alpha$  hydroxylated vitamin D metabolite such as calcitriol along with calcium supplements. This is important because elevated PTH levels in patients with PHP could cause increased bone remodelling and can lead to hyperparathyroid bone disease<sup>5</sup>. In our case child was managed with calcitriol (0.25  $\mu$ g/day) along with calcium supplements and child responded well with normal serum calcium and phosphorus levels and was seizure free. But long term follow up is required to know the exact nature of disease as PHP sometimes are transient.

## Conclusion

PHP is a disease of rare occurrence though exact incidence is not documented worldwide. So a case of resistant hypocalcemia and raised parathormone levels should raise suspicion of PHP. Administration of oral calcium and 1 alpha hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment. The goals of therapy are to maintain serum total and ionized calcium levels within the reference range to avoid hypercalciuria and to suppress PTH levels to normal. This is important because elevated PTH levels in patients with PHP could cause increased bone remodeling and can lead to hyperparathyroid bone disease.

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