A Rare Endocrine Disorder Presenting as Recurrent Seizures

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ABSTRACT
Pseudohypoparathyroidism (PHP) refers to a group of distinct inherited disorders. Patients are characterised by signs and symptoms of hypocalcaemia in association with distinctive skeletal and developmental defects. Pseudohypoparathyroidism is an uncommon sporadic or inherited genetic disorder subdivided into several distinct entities (type Ia, Ib, Ic, type II). The present case highlights the difficulty in making diagnosis as the patient completely lacked phenotypic features related to PHP. We stress the importance of a complete biochemical investigation of the calcium phosphate metabolism to recognize typical biochemical alterations associated with this condition [hypocalcaemia, hyperphosphataemia with increased phosphate tubular reabsorption and elevated parathormone (PTH) levels]. As this is an entirely treatable condition, a high index of suspicion for pseudo hypoparathyroidism with hypocalcemic seizures should be maintained even in otherwise asymptomatic adults.

KEY WORDS: pseudohypoparathyroidism, seizures, hypocalcaemia, parathormone

INTRODUCTION:
Pseudohypoparathyroidism is a heterogeneous group of disorders characterised by hypocalcaemia, hyperphosphataemia, increased serum concentration of parathormone, and insensitivity to the biological activity of parathormone. Patients may present with an unusual constellation of developmental and skeletal defects collectively termed Albright's hereditary osteodystrophy. The disease can present at any age. Patients may remain asymptomatic or may demonstrate characteristic physical features with or without signs and symptoms of hypocalcaemia. This case report, describes the spectrum of manifestations of this rare condition presenting as seizures with absence of peculiar features leading to delayed diagnosis and its management. It report also highlights the importance of biochemical investigations other than clinical features for diagnosing PHP.

CASE REPORT:
A 18 year old male, came to the emergency department with complaints of recurrent seizure like episodes since last 4 days. On detailed history, it was discovered that he had a past history of recurrent seizures for the last 5 years inspite of being on multiple antiepileptic medications including phenytoin sodium and sodium valproate. During the seizure like episodes, patient had stiffness of limbs, uprolling of eyeballs with rubbing of chin over hard surface which caused injury over chin. Despite taking antiepileptics, his seizure like episodes could not be controlled. This happened for two times with the patient. The seizure frequency had increased considerably to one episode daily in the last 4 days, and he would have at least 3-4 episodes in a month before the present episode. Patient also revealed that his mother also had stiffness of limbs.

General physical examination was relatively normal. There was no carpopedal spasm or any other signs of tetany like Chvostek's or Trousseau's sign. Fundoscopy was normal. He had no dysmorphic features.

Investigations revealed that his serum calcium was 5.6mg/dl (N 8.4-10.2 mg/dl), PTH 528 pg/ml (N 14 - 72 pg/ml), phosphate 8.2 mg/dl (N 2.44-4.40 mg %), magnesium 1.2 mg% (1-1.4 mg %),
with normal albumin, alkaline phosphatase, renal function test, normal hemoglobin and glucose level with normal sodium and potassium levels. His vitamin D level could not be done due to financial constraints. TLC and DLC levels were also normal. EEG study was normal.

CT scan revealed extensive bilateral basal ganglia calcification and gyriform calcification in frontal lobe, left temporal and right occipital lobe (Figure 1 and 2). With these investigations, after ruling out other causes, possibility of pseudohypoparathyroidism was suggested. The patient was treated with intravenous calcium gluconate, oral calcium carbonate (CaCo3) 500 mg thrice a day and alfalcaldiol 0.5 mcg daily. Patient was discharged and on repeat follow up, his serum calcium level increased to 8.5 mg/dl with no further complains of seizure like episode or stiffness in limbs.

DISCUSSION:

Pseudohypoparathyroidism (PHP) refers to a group of distinct inherited disorders characterised by PTH resistance. Patients are characterised by signs and symptoms of hypocalcaemia in association with distinctive skeletal and developmental defects. Due to biochemical similarities with hypoparathyroidism but associated with high levels of PTH, it was called pseudohypoparathyroidism (PHP).

Pseudohypoparathyroidism is subdivided into several distinct entities (type Ia, Ib, Ic, type II ). The classification is based on signs of ineffective PTH action (low calcium and high phosphate), urinary cyclic adenosine monophosphate (AMP) response to exogenous PTH, the presence or absence of Albrights hereditary osteodystrophy (AHO) and assays to measure the concentration of the GS alpha subunit of the adenylyl cyclase enzyme.  

PHP Type Ia individuals show evidence for AHO with resistance to PTH and other hormones that stimulate adenyl cyclase in their target tissues, such as thyroid stimulating hormone (TSH), gonadotropins and growth hormone releasing hormone (GHRH). PHP Type Ia clinical features collectively termed AHO include short stature, rounded face, brachydactyly, brachymetacarpia (short fourth and fifth metacarpals), centripetal obesity, heterotopic calcifications, and in some cases, mental or developmental delay. Amorphous deposits of calcium and phosphate are found in basal ganglia in one half of patients. These individuals have hypocalcemia, hyperphosphatemia, with deficient urinary cyclic AMP response to administration of exogenous PTH and GS alpha subunit deficiency. 50% activity of GS alpha subunit is found in these individuals.

Type Ib PHP individuals shows resistance to
hydroxyvitamin D to inactive metabolites, resulting in carbamazepine. These antiepileptic medications particularly phenytoin, phenobarbital, and seizure control is long-term antiepileptic therapy, contributed to intractable epilepsy. Our patient presented with extensive bilateral intracranial calcifications involving the basal ganglia and cerebral cortex, which may have asymptomatic. Our patient presented with extensive bilateral calcification of the cerebral cortex.Extensive calcification of the cerebral cortex extending beyond the basal ganglia, however, is a rare finding. When detected on imaging studies, these findings result in a diverse clinical presentation, including seizures, mental deterioration, and Parkinsonism, although some patients may remain asymptomatic. Our patient presented with extensive bilateral intracranial calcifications involving the basal ganglia and cerebral cortex, which may have contributed to intractable epilepsy.

Another factor shown to contribute to loss of seizure control is long-term antiepileptic therapy, particularly phenytoin, phenobarbital, and carbamazepine. These antiepileptic medications induce hepatic microsomal enzymes that convert 25-hydroxyvitamin D to inactive metabolites, resulting in low levels of vitamin D. This leads to low levels of 1,25-dihydroxyvitamin D, impaired absorption of calcium from the intestine, and reduced mobilization of calcium from bone, further exacerbating hypocalcemia. Laboratory results in these patients will show low serum levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and calcium. If a compliant patient on antiepileptic therapy presents with loss of seizure control, clinicians must consider the possibility of antiepileptic induced hypocalcemic seizures. In a patient with PHP who presents with loss of seizure control after previously being stable on antiepileptic therapy, an even further exacerbation of hypocalcemia may occur, resulting in intractable epilepsy. This was of much importance in our patient as he was started on anti epilepsy five years back.

The aim of PHP therapy is to obtain an adequate calcium-phosphate control and to correct the multiple hormonal resistance, when present. Treatment includes the use of vitamin D active metabolites (alfacalcidol and calcitriol,20-50 ng/kg/day given in two doses) and calcium supplementation (intravenous calcium to correct symptomatic hypocalcaemia and then oral calcium administration according to individual response and dietary calcium intake). The goal is to maintain blood calcium between 2.2-2.7 mmol/l (= 8.8-10.8 mg/dl), urinary calcium excretion <4 mg/kg/day, and the urinary calcium/urinary creatinine ratio <0.2. Once the patient has demonstrated a satisfactory response, patient should undergo a biochemical (calcium, phosphorus, PTH, creatinine) and urinary (calcium and creatinine) examination every three months. A strict follow up is essential to adjust the therapeutic dosage and to preserve a difficult biochemical balance.

Competing Interests:
The authors declare that they have no competing interests.

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