Families of Pseudohypoparathyroidism presenting as Seizure

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Abstract

Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders characterized by variable insensitivity to parathyroid hormone. We describe two cases of 22 year male and 24 year female who have typical clinical features of Albright’s hereditary osteodystrophy (AHO). Laboratory investigation revealed evidence of pseudohypoparathyroidism and skeletal survey showed shortening of the metacarpals and metatarsals.

Introduction

Pseudohypoparathyroidism (PHP) is a rare disease and is characterized by variable insensitivity to parathyroid hormone (PTH). Several variants of PHP have been recognized due to molecular defects in the gene (GNAS1), encoding the alpha subunit of the stimulatory G protein (Gsα) which contribute to different forms of the disease i.e. PHP type 1a, PHP type 1b, PHP type 1c and pseudopseudohypoparathyroidism (pseudopPHP)¹ with different phenotypes, genetic findings and pathogenesis. The alpha subunit of the Gs (Gsα) is a signaling protein essential for the actions of PTH and many other hormones. PHP type 1a is the best understood form of the disease and is associated with a constellation of peculiar clinical features collectively termed Albright hereditary osteodystrophy (AHO). Patients with type 1a PHP show only about 50% activity of Gsα subunit.²

Case Report

Case 1

A 22 year man presented to medical emergency room with three episodes of generalized tonic seizure. He had a history of similar episodes with on and off carpopedal spasms and intermittent calf muscle cramps from last 1 year. History of poor memory and concentration, fatigue and on and off constipation was present. He left the school at the age of 10 years. No history of headache, vomiting, fever, diplopia, decreased vision, decreased urine output, chronic diarrhea, jaundice and swelling over face or feet and goiter. No history of usage of antiepileptic or antitubercular drugs.

On examination patient had a pulse rate of 84/min, regular and BP 124/82 mmHg in right arm in supine position. Pallor/ icterus/ cyanosis/ clubbing/ lymphadenopathy were absent. Skin was coarse and dry. Patient had a height of 164 cm (<3rd percentile) and weight of 72 kg (25th percentile) with BMI of 26.77 kg/m². Systemic examination of respiratory, cardiovascular, abdomen and nervous system didn’t reveal any abnormality. Skeletal examination revealed round face, short right 4th metatarsal and right second toe (Figure 1C). He had subcutaneous hard mobile swellings in lateral aspect of right arm and right leg. Chvostek and Trousseau signs were positive. Family history revealed death of his sister at the age of 18 and she was having same phenotype as of the patient. His mother also had short stature with height of 146 cm (<3rd percentile) with BMI of 28 kg/m². His thyroid function tests were normal. Further biochemical investigations revealed serum calcium 6.0 mg/dl (8.7-10.2 mg/dl), serum phosphate 7.3 mg/dl (2.5-4.3 mg/dl), serum proteins 7.9 g/dl (6.7-8.6 g/dl), serum albumin 4.0 g/dl (3.5-5.5 g/dl) with elevated serum PTH 278.8 pg/ml (8-51 pg/ml) and decreased vitamin D 38.43 nmol/L (75-250 nmol/L) levels. Serum magnesium 1.7 mg/dl (1.5-2.3 mg/dl). Twenty four hours urine calcium was 12.08 mg/gm of creatinine and phosphate 96.4 mg/gm of creatinine, fT4 12.6 pmol/L (9.0-16 pmol/L), fT3 4.2 pmol/L (3.7-6.5 pmol/L) were normal with elevated TSH levels of 21.26 mIU/ml (0.34-4.25 mIU/ml). Anti-TPO antibody level was 28 IU/ml (<35 IU/ml). His LH 2.50 U/L (2.0-12.0 U/L), FSH 3.94 IU/L (1.0-12.0 IU/L) and testosterone 14.4 nmol/L (9.36-37.10 nmol/L) levels were within normal range. ECG showed prolonged QTc interval of 0.514 ms. Fundus was normal. Radiograph of the hands and feet showed marked shortening of right fourth metacarpal (Figure 1B) and left fourth metatarsal with shortening of right second toe (Figure 1D). Radiograph of right arm showed subcutaneous calcified depositions at lateral aspect of mid of the arm and skull showed subcutaneous calcified depositions (Figure 1E). IQ was 68 (mild intellectual impairment). Ultrasound KUB didn’t show any nephrocalcinosis. NCCT brain was normal.

His mother had heterotopic calcifications at the base of bilateral first metacarpals which was confirmed on Xray of hands. His parents were having normal values of serum calcium, phosphate, albumin and alkaline phosphatase.

In this case typical clinical features of AHO with evidence of hypocalcemia, hyperphosphatemia, elevated PTH level (secondary to decreased levels of vitamin D and resistance to PTH), normal renal function with strong family history (in his sister) suggested the diagnosis of PHP. Patient is on oral calcitriol 1 mcg/day with oral calcium carbonate 500 mg thrice daily and levo-thyroxine 100 mcg/day (sign and symptoms of hypothyroidism with TSH >10 mIU/ml). Patient didn’t have any seizure episode after starting treatment.

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and his biochemical picture (serum calcium 7.4 mg/dl, phosphate 6.0 mg/dl) improved after 2 weeks of treatment.

Case 2

A 24-year old married female presented to emergency department with status epilepticus. She was apparently all right till 2-3 years of age, when she developed recurrent generalized tonic-clonic seizures. She was treated with alternative system of medicine and later on with antiepileptic drugs, but seizures were never controlled. She had a history of poor memory and concentration. She left the school at the age of 7 years. She attained menarche at the age of 14 and had a history of irregular menstrual cycles since menarche. She had been married for 2 years and had not conceived till date. Her mother had a similar illness.

On examination patient had a pulse rate of 76/min, regular and BP of 116/74 mmHg in right arm in supine position. Pallor/ icterus/ cyanosis/ clubbing/ lymphadenopathy were absent. Her height was 144 cm (<3rd percentile), weight 53 kg (15th percentile) with BMI of 25.65 kg/m². She had a round face, short bilateral fourth metacarpals and metatarsals (Figures 2A, B), dental caries and dental malocclusion. Her mental assessment was suggestive of moderate mental retardation (IQ-40). Biochemical investigations showed hypocalcaemia 5.2 mg/dl (8.7-10.2 mg/dl), hyperphosphatemia 6.8 mg/dl (2.5-4.3 mg/dl), serum proteins 7.2 g/dl (6.7-8.6 g/dl), serum albumin 4.1 g/dl (3.5-5.5 g/dl), raised PTH level 166.6 pg/ml (8-51 pg/ml), Vitamin D 90.54 nmol/L (75-250 nmol/L). Serum magnesium 1.6 mg/dl (1.5-2.3 mg/dl). Twenty four hours urine calcium was 10.8 mg/gm of creatinine and phosphate 106.6 mg/gm of creatinine, fT4 13.4 pmol/L (9.0-16 pmol/L), fT3 4.8 pmol/L (3.7-6.5 pmol/L) with elevated TSH levels of 10.2 mIU/L (0.34-4.25 mIU/L). Anti-TPO antibody level was 30 IU/ml (<35 IU/ml). Her LH 5.60 U/L (2.0-12.0 U/L), FSH 4.67 IU/L (1.0-12.0 IU/L) and testosterone 12.89 nmol/L (9.36-37.10 nmol/L) levels were within normal range. ECG showed prolonged QTc interval of 0.548 ms. Her complete hemogram, liver and renal function tests were within normal range. Non-contrast computerized tomography of brain showed bilateral basal ganglia calcification and calcification at grey-white matter junction (Figure 3). Ultrasound examination of abdomen and pelvis was normal with no evidence of nephrocalcinosis. His parents were having normal values of serum calcium, phosphate, albumin and alkaline phosphatase.

In view of AHO phenotype, heterotopic calcification, hypocalcaemia, hyperphosphatemia, raised PTH a diagnosis of PHP was made. Patient was initially treated with intravenous calcium followed by oral calcium and calcitriol. Patient improved after treatment and is now seizure free.

Discussion

Pseudohypoparathyroidism refers to a heterogeneous group of disorders characterized by
parathyroid hormone (PTH) resistance. Pseudohypoparathyroidism is an uncommon sporadic or inherited genetic disorder subdivided into several distinct entities (type Ia, Ib, Ic, type II). All subtypes are caused by mutation or imprinting abnormalities in the stimulatory G protein (G_s). The present case reports highlight the variable and rare phenotypic presentation of pseudohypoparathyroidism.

History of seizures with hypocalcemia, hyperphosphatemia with elevated PTH levels would suggest chronic renal failure (commoner cause) or pseudohypoparathyroidism (rare cause), so if we rule out chronic renal failure the only differential diagnosis left is pseudohypoparathyroidism.

Another interesting finding in both cases is finding of subclinical hypothyroidism since there can be resistance to many peptide hormones including thyroid-stimulating hormone (thyrotropin), antidiuretic hormone, gonadotropins, glucagon, adrenocorticotropic, and growth hormone–releasing hormone which use the alpha subunit of stimulatory G protein to enhance cAMP production.  

The dominant pattern of inheritance of PHP type 1a has been attributed to haploinsufficiency of GNAS1, meaning that the protein produced by a single normal G_s allele cannot support normal function, although it may suffice for survival. The single normal G_s allele preserves the responses to hormones such as corticotropin and glucagon. The haploinsufficiency of the GNAS1 gene is tissue specific, which may explain the selective resistance to hormones and the characteristic habitus of patients with PHP type 1a.  

GNAS1 is imprinted in humans so that expression of the allele for a specific tissue is dependent on whether the allele is maternally or paternally inherited. Thus, maternal or paternal transmission leads to different disease manifestations. Heterozygous loss of function mutations in the G_s gene inherited from the mother lead to PHP 1a, whereas the same mutation inherited from the father leads to pseudoPHP, a distinct entity characterized by AHO, without evidence of hormone resistance.  

Patients with PHP type 1b lack features of AHO, have normal expression of Gsa protein in accessible tissues, and manifest hormonal resistance limited to PTH target tissues. PTH resistance may be limited to the kidney, with PTH responsiveness preserved in the bone, as evidenced by the hyperparathyroid skeletal lesions observed in these patients.  

Two other variants of PHP, PHP type 1c and PHP type 2, are much less characterized than are the other forms of PHP. Patients with PHP type 1c do not have a detectable defect in G_s protein despite having clinical and laboratory findings similar to those observed in patients with PHP type 1a.

Patients with PHP type II like PHP type 1b have hypocalcaemia, hyperphosphataemia and increased serum PTH, but they lack the physical features associated with AHO. Unlike patients with type 1b, however, they demonstrate a normal urinary cAMP response.  

PHP type 1a and 1c are usually associated with a constellation of peculiar clinical features collectively termed Albright hereditary osteodystrophy (AHO) including short stature, stocky habitus, obesity, development delay, round face, dental hypoplasia, brachymetacarpals, brachymetatarsals, soft tissue calcification or ossification. But the presence of all these phenotypic aspects is rare.  

Assessment of skeletal and renal responsiveness to PTH is accomplished by measurement of changes in serum calcium, phosphorus, cAMP, and calcitriol concentrations and in urinary cAMP and phosphorus excretion after administration of the biosynthetic N-terminal fragment of PTH. This test is done mainly in research laboratories and is not available commercially.

Radiography of the hand may show a specific pattern of shortening of the bones, in which the distal phalanx of the thumb and the third through fifth metacarpals are shortened. Radiography may also show small soft tissue opacities suggestive of metastatic calcifications. Computed tomography (CT) scanning may reveal calcification of the basal ganglia. Analysis of the GNAS1 gene helps to identify the specific genetic defect in patients with PHP type 1a.

Treatment of PHP is similar to that of hypoparathyroidism. 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.

Variability in response makes it necessary to establish the optimal regimen for each patient, based on maintaining the appropriate blood calcium level and urinary calcium excretion.

**Conclusion**

These cases emphasize that initial clinical onset may be related to a severe hypocalcaemia leading to seizures. The diagnosis of this rare hereditary condition is often delayed, leading to an initially inappropriate approach and therapy. So it is extremely important to perform a complete biochemical analysis (that includes serum calcium, phosphate, magnesium and parathyroid hormone measurements) in order to distinguish PHP from other disorders. The elevated serum concentration of PTH in a patient with chronic hypocalcemia, hyperphosphatemia, and normal renal function excludes hypoparathyroidism and chronic renal failure, hence suggests the presence of pseudohypoparathyroidism.

**References**