Pseudohypoparathyroidism type IA and II with severe neuropsychic manifestations

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Pseudohypoparathyroidism (PHP) is characterized by unresponsiveness of target tissues to the biological actions of the parathyroid hormone (PTH), with resulting hypocalcemia and hyperphosphatemia, despite the elevated serum levels of PTH. PHP is divided into types Ia, b, c and II, depending on the presence of Albright's hereditary osteodystrophy (AHO), defective urinary excretion of phosphate (U-P) and response in urinary excretion of cyclic adenosine monophosphate (U-cAMP) after the administration of exogenous PTH. Patients with PHP might exhibit various manifestations of neuropsychic disturbances. We present two boys, aged 14 and 16 years, both with paresthesia, anxiety and epilepsy; the former patient also suffered from mild mental retardation. In both patients, hypocalcemia and hyperphosphatemia together with increased serum levels of PTH suggested the diagnosis of PHP. After administration of exogenous PTH (Ellsworth-Howard test), there was a drop in U-P in both patients, while U-cAMP was decreased in the first patient and increased in the second one, thus confirming the diagnoses of PHP Ia and II, respectively. Neuropsychic disturbances and epilepsy resolved completely in both patients after treatment with calcium and dihydrotachysterol. Evaluation of calcemia and phosphatemia should be mandatory in all patients with neuropsychic disorders. Ellsworth-Howard test remains a useful tool in the differential diagnosis of PHP.

Key words: hypocalcemia, parathyroid hormone, pseudohypoparathyroidism, epilepsy.

Pseudohypoparathyroidism (PHP) is represented by a heterogeneous group of disorders, whose common feature is resistance to biological actions of the parathyroid hormone (PTH). Most patients with PHP are hypocalcemic and hyperphosphatemic, despite elevated concentrations of PTH in plasma. Clinical features and location of the putative defect causing hormone resistance permit separation of PHP in types I and II, the former divided into subtypes a, b and c[1-3]. PHP types I and II are distinguishable by different responses in urinary cyclic-adenosine monophosphate (U-cAMP) after administration of exogenous PTH (Ellsworth-Howard test)[1-3]. Although it is possible to provide proper treatment without differentiating between the various types of PHP, genetic counseling and full understanding of the rare forms of these syndromes require testing of renal responsiveness to PTH[1,3]. We report two boys with severe neuropsychic disturbances together with hypocalcemia and hyperphosphatemia, where diagnosis of PHP types Ia and II was established. The neuropsychic disorders resolved after correction of calcemia.

Case Reports

Case 1

A 14-year-old boy had been treated unsuccessfully since the age of 11 years for grand mal epilepsy, mild mental retardation (IQ = 67) and manifest tetany. Due to accidentally revealed hypocalcemia (ionized Ca 0.7 mmol/L, ni 1.0-1.15 mmol/L) and hyperphosphatemia (2.83 mmol/L, n: 0.8-1.6 mmol/L), he was referred to our department. The boy had a very round face without any other dysmorphic features or deformities of the

extermities. On admission his height was 174 cm (+0.5 SD) and weight 60 kg (+0.27 SD). The serum concentrations of natrium, potassium and magnesium were within normal reference ranges, as were the serum activities of alkaline phosphatase and aminotransferases. Computed tomography (CT) of the brain revealed calcifications in the basal ganglia (Fig. 1). X-ray of the chest and echocardiography were normal, without any signs of calcification. The X-ray of his hand revealed normal bone age and no signs of brachymetacarpia. Treatment was immediately started with perorally administered calcium citrate (1000 mg Ca/day) and dihydrotachysterol (2 x 0.5 mg/day). The serum levels of ionized calcium reached 1.1 mmol/L within six days upon the initiation of the therapy. No further grand mal seizures occurred. The serum levels of intact parathyroid hormone (S-PTH) were repeatedly measured by radioimmunoassay (RIA) after the initiation of the treatment and always exceeded the upper reference range (14 and 14.7 pmol/L, n: 0.7-5.5), suggesting the diagnosis of PHP. Therefore, a modified Ellsworth-Howard test was performed to distinguish the type of PHP[2]. After the first morning void, the fasting patient ingested 200 ml of water and urine was collected, both one hour prior to the 10 minute infusion of 200 units of synthetic polypeptide hormone consisting of the 1-34 fragment of human PTH (Parathar-Rorer Pharmaceuticals), and at the 0-30 minute and 30-60 minute postinfusion time periods. Blood was collected prior to the Parathar infusion and at 10 and 60 minutes' postinfusion for the evaluation of serum phosphate (5-P) and creatinine. The urinary phosphate (U-P), creatinine (U-Cr) and U-cAMP excretion was measured. The U-cAMP results were corrected for U-Cr. The tubular maxiumm of phosphate/glomerular filtration rate (TmP/GFR) was obtained using a relationship derived by Walton and Bijvoet[4]. There was a decrease in both U-cAMP and U-P levels, with increased TmP/GFR (Table I), therefore the diagnosis of PHP Ia was established. The boy has been followed in our department for four years, receiving daily doses of 1000-1500 mg of calcium and 1 mg of dihydrotachysterol. Currently, he is in a good state of health, both physically, with no more seizures, and mentally (IQ = 84).

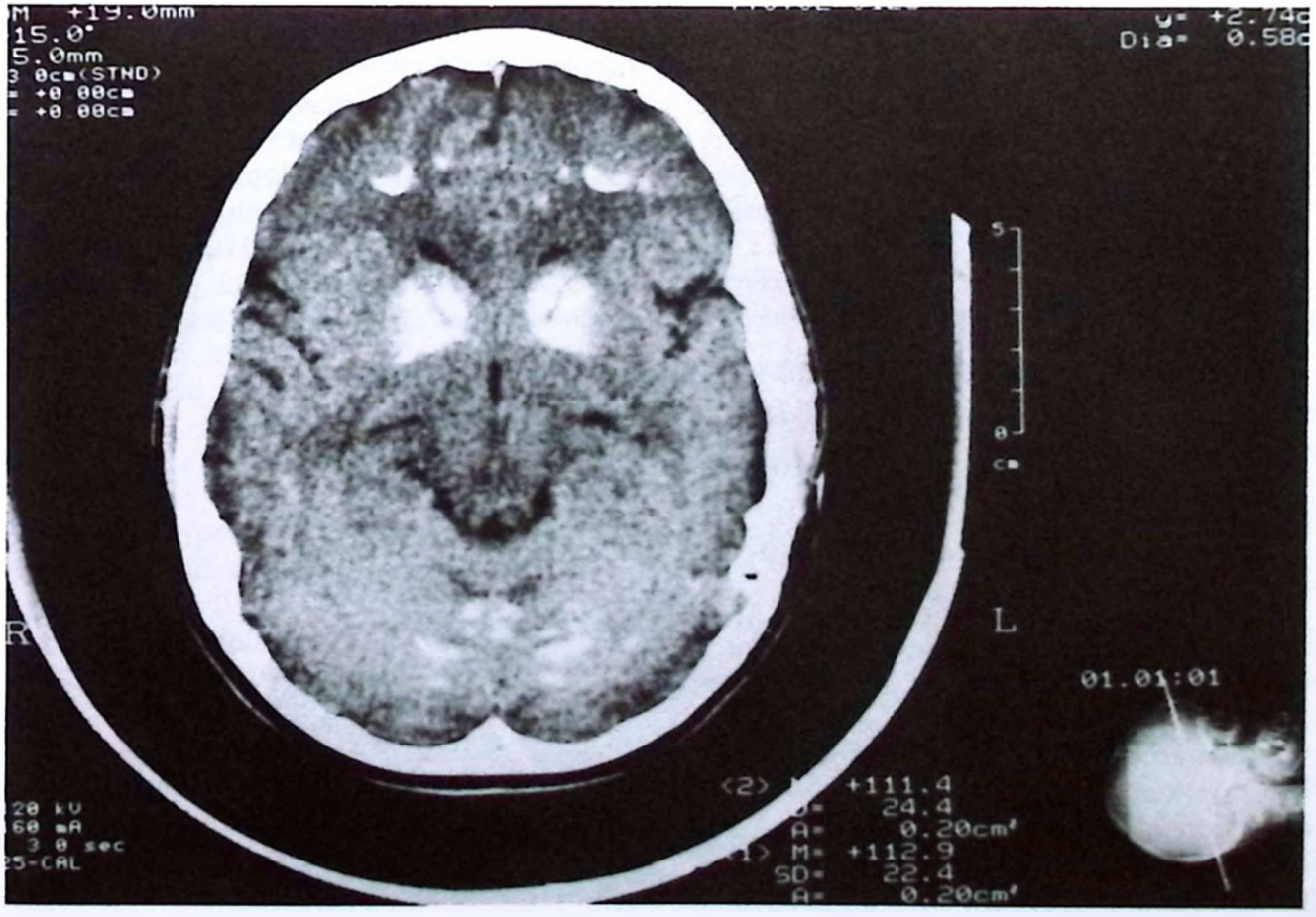

Fig. 1. Calcifications in basal ganglia as revealed by CT.

Table I. Changes in TmP/GFR (mmol/L) and U-cAMP (nmol/mg of creatinine) During the First Hour After Infusion of PTH (1-34)

	Baseline		30 minutes		60 minutes	
Time	TmP/GFR	U-cAMP	Tmp/GFR	U-cAMP	TmP/GFR	U-cAMP
Case 1	2.90	5.90	4.85	0.80	4.45	0.60
Case 2	3.10	4.10	3.50	66.80	3.30	42.20

TmP/GFR : tubular maximum of phosphate/glomerular filtration rate.
U-cAMP : urinary cyclic-adenosine monophosphate.
PTH : parathyroid hormone.

Case 2

A 16-year-old boy with normal physical appearance was admitted with history of recurrent faintings since the age of 11, and an intractable pain of the cervical spine. Those symptoms were erroneously diagnosed as epilepsy and cervicocranial syndrome. Calcemia was never assessed before he reached our department. On admittance, he was pale and exhausted, showed signs of ataxia and manifest tetany, and complained of diplopia, paresthesia, anxiety and severe pain of the neck. Biochemical evaluation revealed severe hypocalcemia (ionized Ca 0.667 mmol/L), hyperphosphatemia (S-P 4.2 mmol/L), hypocalciuria and hypophosphaturia. The serum concentrations of natrium, potassium and magnesium were within normal reference ranges, as were the serum activities of alkaline phosphatase and aminotransferases. Additional abnormal findings included calcification of basal ganglia revealed by computed tomography (Fig. 2) and mild cortical cataract. Abdominal sonogram showed bilateral nephrocalcinosis. There were normal findings on the X-ray of the chest and echocardiography. The boy received immediately intravenous infusion of 10 percent calcium gluconate (1.5 ml/kg/day) and calcitriol (2x0.25 µg/day). Within the first day his state improved dramatically, and all symptoms disappeared within 10 days. The serum concentration of ionized calcium reached the reference level of 1.1 mmol/L on day 8. The intravenous administration of calcium was replaced on the third day by peroral supplementation of calcium citrate (1000 mg Ca/day). S-PTH was measured by RIA before and after the normalization of serum calcium levels and repeatedly exceeded the upper reference range (9 and 10 pmol/L, n: 0.7-5.5). The combination of severe hypocalcemia and elevated S-PTH suggested the diagnosis of PHP. Therefore, the modified Ellsworth-Howard test was performed. There was a decrease in U-P reflected by an increase in TmP/GFR, and a 16-fold increase in U-cAMP after the PTH infusion (Table I). The diagnosis of PHP type II was established in this patient. He has been followed for five years in our department, with an uneventful course, receiving daily doses of calcium (1500-2000 mg) and dihydrotachysterol (2x0.5 mg). No neurologic problems have occurred since the normalization of calcemia.

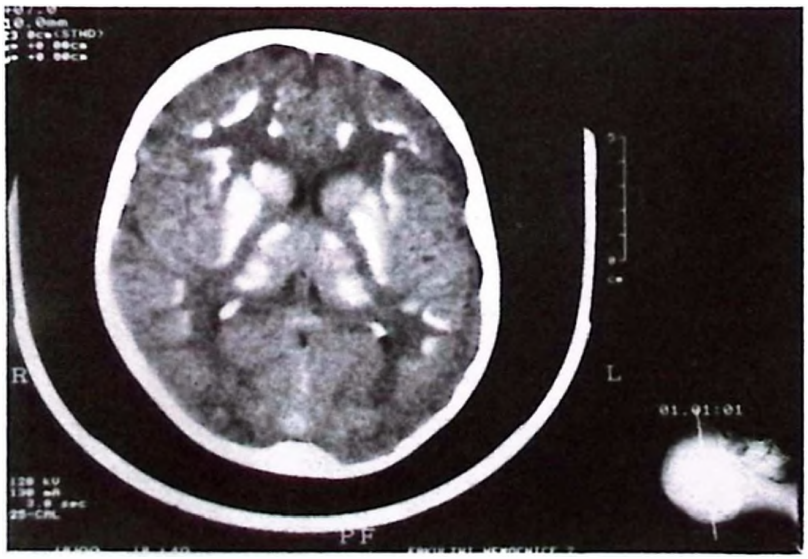

Fig. 2. Calcifications in basal ganglia as revealed by CT.

Parents of both patients had normal physical appearance and normal calcemia and phosphatemia.

Discussion

Parathyroid hormone plays an essential role in the maintenance of calcium and phosphate homeostasis by mobilizing calcium from bone to the extracellular fluid and by increasing urinary phosphate excretion and enhancing renal calcium reabsorption. Furthermore, PTH stimulates conversion of 25-OH-vitamin D to 1,25 $(OH)_2$ vitamin D, thus controlling intestinal calcium absorption[1,3].

Under physiological conditions, the PTH binds to its specific cell-surface receptor. Activated receptor interacts with one or more members of a family of guanine nucleotide binding proteins (G-proteins) to facilitate release of guanosinediphosphate (GDP) and binding of guanosinetriphosphate (GTP). GTP-bound G-proteins in turn interact with specific effectors that catalyze formation of intracellular second messengers, including cAMP, which mediates the phosphaturic and bone resorptive actions of PTH and is the most probable second messenger of PTH action on 1-alfa hydroxylase. The formation of cAMP from ATP and Mg is catalyzed by adenyl cyclase, which is under dual regulation by distinct G proteins, both stimulatory (Gs) and inhibitory (Gi)[1,5].

Defects at different sites in the PTH response pathway result in end-organ resistance to PTH, and are responsible for distinct foms of PHP. Defects proximal to cAMP production result in PHP type I, while defects distal to cAMP generation result in PHP type II. Biochemical abnormalities in all types of PHP include hypocalcemia, hyperphosphatemia and hypophosphaturia with normal renal function. On physical examination, patients exhibit symptoms of neuromuscular irritability secondary to hypocalcemia, such as paresthesia, latent and manifest tetany, and seizures. Mood disorders may be present[6]. Other features include dental defects (enamel hypoplasia), cataracts and calcifications in subcutaneous tissue, in basal ganglia and in the myocardium[1,3,5,7-9]. Hypocalcemia may not be evident immediately in the neonatal period, but usually becomes symptomatic within the first ten years of life, sometimes even later[9,10].

Pseudohypoparathyroidism type I can be further divided in PHP type Ia, Ib and Ic. PHP type Ia is a familial form with Gs protein deficiency which is maped to the distal long arm of chromosome 20. Inheritance is autosomal dominant[1,11]. Clinical features include Albright's hereditary osteodystrophy (AHO) with short stature, obesity, rounded face, short stubby fingers, and shortened metacarpals and metatarsals[1,3,8], all of which may be the result of premature skeletal maturation and closure of epiphyses[12]. Other symptoms include mild mental retardation, headaches, and olfactory and sensorineural hearing dysfunction[1,3], which might be attributed to chronic hypocalcemia. Several other endocrinopathies including growth hormone deficiency and resistance to thyrotropin, gonadotropin and glucagon have been described in patients with PHP Ia[1,3,13] and have been postulated as results of Gs protein deficiency[1,13,14]. Soft tissue calcifications and mental deficiency are typical signs of PHP Ia[5]. However, in some patients with PHP Ia, many of these features may be subtle or absent[14].

Pseudopseudohypoparathyroidism (PPHP) consists of AHO with normal biochemical values, including serum calcium (S-Ca) and S-PTH. Genetic linkage between PHP Ia and PPHP has been proposed. concerning variable expressivity of the Gs protein deficiency[1].

In PHP type Ib, physical appearance is normal and resistance is limited to PTH, with similar biochemical properties and similar neurologic and mental symptoms as in PHP Ia, but with normal Gs protein activity[5]. Round face, soft tissue calcifications, brachymetacarpia and mental deficiency never occur in PHP Ib[5]. PHP Ib may be both familial and sporadic[1,3,5]. Pseudohypoparathyroidism type Ic is represented by AHO, generalized hormone resistance, normal Gs protein activity and hypocalcemia. Inheritance and molecular defect remain unknown[3]. PHP Ia, b, c are all characterized by impaired phosphaturic and U-cAMP response to exogenous PTH.

Pseudohypoparathyroidism type II is characterized by impaired phosphaturic response and normal U-cAMP response after the application of exogenous PTH. The physical appearance is normal in 50 percent of the patients with PHP II. Soft tissue calcifications, small stature,, obesity, mental deficiency and seizures might occur in 50 percent of patients with PHP II, while round face has never been observed[5].

A case of PHP II associated with Bartter's syndrome has been reported[15]. PHP II is considered a rare acquired disease[1,3]. PHP types I and II have been described in different family members[6]. The clinical findings as revealed by a multicenter study of 71 children with PHP[5] are summarized in Table II.

Findings similar to PHP II have been described in some patients with severe vitamin D deficiency, as U-cAMP was normal and U-P defective after PTH infusion[16]. Clinical studies have reported end-organ resistance to PTH action in hypocalcemic patients with magnesium deficiency, with either normal or blunted U-cAMP response to exogenous PTH[17]. The bone remodeling response to PTH is relatively intact in many patients with PHP, however, bone resorption may exceed bone formation, resulting in osteopenia, especially in patients with PHP Ib[14,18,19]. Treatment of all types of PHP is lifelong and rests in the application of calcium and vitamin D, while closely monitoring calcemia and calciuria to avoid under or over-treatment[1].

Table II. Clinical Findings in 71 Children with PHP

Clinical findings	PHP Ia (n = 45)	PHP Ib (n = 8)	PHP Ic (n = 6)	PHP II (n = 2)	PPHP (n = 10)
Seizure %	38	0	66.7	50	0
Subcutaneous calcification %	42.3	0	16.7	50	50
Soft tissue calcification %	41	0	66.7	50	0
Brachymetacarpia %	86.7	0	66.7	0	80
Round face %	82.3	0	66.7	0	90
Height < SD %	38.4	0	0	50	88.9
Weight > SD %	48.5	0	40	0	0
Weight excess %	64	0	40	50	12.5
Mental deficiency %	40	0	40	50	40

Adapted from Marguet et al.[5].
PHP : pseudohypoparathyroidism.
PPHP : pseudopseudohypoparathyroidism.

The differential diagnosis of PHP types I and II rests in the evaluation of U-P and U-cAMP after intravenous application of 200 units of exogenous PTH 1-34. While there is no increase in U-P (therefore no decrease in TmP/GFR) in either PHP I or II, there is at least a six-fold increase in U-cAMP (nmol/mg of creatinine) in PHP type II 30 minutes after the PTH infusion, with no increase of U-cAMP in PHP Ia, or b[2] (Table III).

Table III. Differential Diagnosis of PHP

Diagnosis	AHO	S-Ca	S-P	S-PTH	Gs protein activity	U-P	U-cAMP (after PTH)
PHP Ia	Yes	Low	High	High	Low	Low	Low
PHP Ib	No	Low	High	High	Normal	Low	Low
PHP Ic	Yes	Low	High	High	Normal	Low	Low
PHP II	No	Low	High	High	Normal	Low	High
PPHP	Yes	Normal	Normal	Normal	Low	Normal	High
HP	No	Low	High	Low	Normal	Low	High

OH : Albright's hereditary osteodystrophy.
S-Ca : serum calcium.
S-P : serum phosphate.
S-PTH : serum parathyroid hormone.
Gs : G (stimulatory).
U-P : urinary phosphate.
U-cAMP : urinary cyclic-adenosine monophosphate.
PHP : pseudohypoparathyroidism.
PPHP : pseudopseudohypoparathyroidism.
HP : hypoparathyroidism.

Case 1 had a rounded face, intracerebral calcifications, mental deficiency, seizures, hypocalcemia, hyperphosphatemia, elevated S-PTH and blunted response in U-P and U-cAMP after the PTH infusion, all compatible with the features of PHP Ia[5] (Tables I-III).

In Case 2, normal physical appearance, severe hypocalcemia and hyperphosphatemia, together with neuropsychic symptoms, cataracts and soft tissue calcifications in the basal ganglia and kidneys, high S-PTH and physiological U-cAMP response to infusion of exogenous PTH pointed to the rare diagnosis of PHP II. In both patients, the S-PTH remained elevated even after the correction of calcemia, thus ruling out vitamin D deficiency. Serum magnesium concentrations were normal in both patients. There were no signs of subcutaneous or cardiac calcifications.

In conclusion, we reported two patients with PHP who were originally erroneously diagnosed as epilepsy. This resolved after the normalization of calcemia. Therefore, the evaluation of calcemia should be mandatory in all patients with various neurologic and mental disorders and psychomotor retardation. Elevated S-PTH in the presence of hypocalcemia suggests the diagnosis of PHP. The modified Ellsworth-Howard test remains the most useful tool in arriving at such a diagnosis and helps to differentiate between PHP types I and II.

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