Case Report

A Case of Pseudohypoparathyroidism Type 1 Associated with Gonadotropin Resistance and Hypercalcitoninaemia.

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A case of a thirty-eight year old man with pseudohypoparathyroidism (PHP) type 1 associated with gonadotropin resistance and hypercalcitoninaemia was reported. The basal levels of the luteinizing hormone and follicle-stimulating hormone were elevated, and the responses to the luteinizing hormone-releasing hormone were exaggerated. The basal level of testosterone was normal, but the response to human chorionic gonadotropin was blunted. The serum calcitonin level was high, and hyper-responsiveness was observed by pentagastrin administration. From these results, it was suggested that partial testicular resistance to gonadotropin and the possibility of resistance to calcitonin were present in our case.

Key Words: Pseudohypoparathyroidism, Hypogonadism, Adenylate cyclase, Guanine monophosphate regulatory unit, Hormone resistance

Pseudohypoparathyroidism (PHP) type 1 is a hereditary disorder characterized by the biochemical features of hypoparathyroidism (hypocalcemia and hyperphosphatemia), peculiar somatic phenotypes (a round face, short stature, short metacarpus and metatarsus, referred to as Albright's hereditary osteodystrophy) and target organ resistance to the parathyroid hormone (PTH)¹⁾.

Recently, it has been shown that resistance to PTH is caused by a defect in the guanine monophosphate regulatory unit (G unit) within the membrane-bound hormone-receptor adenylate cyclase complex that produces 3'-5'-cyclic adenosine monophosphate (cyclic AMP)^{2,3)}.

Furthermore, resistance to hormones were found not only to PTH but also to other hormones such as gonadotropins^{4,5)}, the thyroid-stimulating hormone (TSH)^{3,5-8)}, and the antidiuretic

hormone (ADH)⁹⁾. Furthermore, a prolactin (PRL) deficiency¹⁰⁾, an abnormal growth hormone (GH) response¹¹⁾ were also reported in patients with PHP type 1. Since the G unit is common to all tissue, as opposed to a hormone receptor which is specific to each hormone, this simultaneous resistance to various hormones shown in PHP type 1 can be explained by the defect in the G units in the affected target endocrine organs¹⁻³⁾.

We have described a patient with PHP type 1 associated with gonadotropin resistance and hypercalcitoninaemia. As far as we know, there is no information available on this combination of hormonal abnormalities.

CASE REPORT

A thirty-eight year old man was admitted to our department for an evaluation of abnormal

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calcification observed in a head X-ray which had been taken during an examination of a minor facial injury caused by a traffic accident one month before admission. His parents and their six children had never had any history of tetany and convulsive seizure, and no disturbances in somatic abnormalities. His parents were not consanguineous. He was born at full term, and had no abnormalities during the entire course of pregnancy and delivery. He had never experienced convulsive seizures or tetany. At the age of twenty five, bilateral cataract were surgically treated. He got married at the age of twenty three, and had three children, none of whom had somatic abnormalities. He was still sexually active at the time of admission.

A physical examination revealed a short stature and mild obesity (height 147 cm, body weight 50 kg). His blood pressure was 140/80 mmHg, pulse rate was 72 beats/min. He had a round face and short neck, and did not have any abnormalities in his fingers and toes. Both Chvostek's and Trousseau's signs were negative. The eyes were post-operative aphakia. The thyroid gland was not enlarged. His external genitalia appeared to be normal and his testes were not atrophic. No abnormal findings were noted in his chest and abdomen. A neurological examination showed that he was normal, except for mild mental retardation. No abnormalities were found in ultrasonic examinations of the thyroid and abdomen, nor in upper gastrointestinal examinations using barium.

The laboratory data are shown in Tables 1 and 2. Serum calcium was 3.6 mEq/l, while serum

phosphate was 5.2 mEq/l. Blood urea nitrogen, creatinine, creatinine clearance, arterial blood gas, an electrocardiogram and electroencephalogram were all normal. The computerized tomography of the brain showed marked calcifications in the basal ganglia, frontal lobes and dentate nuclei. Other ectopic calcifications were not found in the X-ray examinations.

The serum PTH levels measured by C terminal, midportion and N terminal assays were normal. While plasma 25-hydroxycholecalciferol ($25(\text{OH})\text{D}_3$) was normal, 1,25-dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$) was lower than the normal range (Table 2). Neither urinary cyclic AMP nor phosphate excretions were increased by i.v. administration of 100 units of synthetic 1-34 PTH (Ellsworth-Howard test).

The thyroid hormones, a glucose tolerance test and the adrenal hormones were all normal. The

Table 1. Laboratory data

Hemogram		TP	7.6 g/dl
RBC	$448 \times 10^4/\text{mm}^3$	A/G	1.34
Hb	13.7 g/dl	Alb	57.3%
Ht	42.3%	Globulin	α_1 3.8%
WBC	$4300/\text{mm}^3$		α_2 9.6%
Plt	$23.5 \times 10^4/\text{mm}^3$		β 8.9%
Urinalysis			γ 20.2%
Protein	(-)	BUN	15 mg/dl
Sugar	(-)	UA	4.7 mg/dl
Sediment	normal	CRTNN	1.0 mg/dl
Creatinine clearance	100 ml/min		
Blood chemistry		GOT	22 IU/l
Na	142 mEq/l	GPT	14 IU/l
K	4.1 mEq/l	LDH	342 IU/l
Cl	106 mEq/l		
Ca	3.6 mEq/l		
IP	5.2 mEq/l		
Mg	1.9 mEq/l		

Table 2. Laboratory data (2)*

PTH-C	0.91 ng/ml (0.20-1.00)	T_3	102 ng/dl (84-162)
PTH-MID	0.52 ng/ml (<0.80)	T_4	5.1 $\mu\text{g}/\text{dl}$ (5-13)
PTH-N	0.30 ng/ml (<0.60)	TSH	4.7 $\mu\text{U}/\text{ml}$ (<5)
$1,25(\text{OH})_2\text{D}_3$	10.5 pg/ml (20-60)	PRL	3.9 ng/ml (2-20)
$25(\text{OH})\text{D}_3$	25.6 ng/ml (14-42)	ACTH	20 pg/ml (15-85)
		GH	1.5 ng/ml (<5)
CT	310 pg/ml (<160)	LH	93 mIU/ml (6.5-34.5)
		FSH	57.1 mIU/ml (1.9-21.8)
PRA	1.2 ng/ml/hr (0.7-1.5)		
Cortisol	10 $\mu\text{g}/\text{dl}$ (7-12)		
PAC	50 pg/ml (10-70)		

* Numbers in parentheses are normal values of his age in our hospital.

basal levels of TSH, PRL, GH, the adrenocorticotrophic hormone (ACTH) and the responses of these hormones to provocation tests by the thyrotropin releasing hormone or 1-DOPA or insulin-induced hypoglycemia were also within the normal range (Table 2).

The basal levels of both the luteinizing hormone (LH) and the follicle-stimulating hormone (FSH) were almost three times higher than normal (Table 2), and the response to the luteinizing hormone releasing hormone (LH-RH)

were exaggerated (Figure 1). Furthermore, the basal level of testosterone was normal for his age (Table 2), the response to an human chorionic gonadotropin (HCG) injection (5000 units/day for three days) was blunted (488 ng/dl before and 800 ng/dl after stimulation).

Finally, the serum calcitonin (CT) level was high despite hypocalcemia (Table 2), and hyper-responsiveness was observed by pentagastrin (0.5 μ g/kg i.v.) administration (Figure 2).

He received 2-3 μ g of 1 α hydroxy-D₃ per day and his serum calcium and phosphate levels normalized. One year after admission, he remained normocalcemic on 2 μ g of 1 α hydroxy-D₃, and no abnormalities were found in physical and routine laboratory examinations.

DISCUSSION

The present case had classic somatic and biochemical abnormalities of PHP, while the serum PTH level was normal, and PTH administration failed to increase urinary cyclic AMP and phosphate excretions in the Ellsworth-Howard test. The present case was therefore classified as type 1 of PHP.

The endocrine abnormalities seen in the present case are very interesting with evidence of disturbances in two different endocrine systems. Although resistance to TSH^{3,5-7)}, a prolactin deficiency¹⁰⁾, an abnormal GH response¹¹⁾, and ADH resistance⁹⁾ have been described in patients with PHP type 1, normal functions were, however, observed in the pituitary-thyroid, pituitary-adrenal cortex, GH and PRL in the present case.

A comparable disorder of pituitary testicular dysfunction was present. The presence of elevated basal levels of LH and FSH compared to those of a normal adult male, exaggerated gonadotropin responses to LH-RH administration and a poor response of testosterone to HCG are consistent with testicular resistance to gonadotropin. However, this resistance was not complete, because his external genitalia had developed normally, the basal testosterone level was normal for his age, and finally, he was still sexually active at the time of admission. Since none of the cases under the age of forty developed hypergonadotropinemia in the study carried out by Stearns et al.¹²⁾, it seems

Fig. 1. Responses of LH and FSH to LH-RH administration (100 μ g).

Fig. 2. Response of CT to pentagastrin administration (0.5 μ g/kg).

unlikely that this resistance was due to aging itself.

The other abnormality was an increased serum concentration of CT and hyper-responsiveness to pentagastrin administration. It is well known that CT levels are increased in medullary thyroid carcinoma, the Zollinger-Ellison syndrome, bronchogenic carcinoma and in many other types of tumor¹³). However, there was no evidence of tumors in this patient at least during our observation period of one year. It therefore seems possible that the increase in serum CT could not be derived from undiagnosed tumors. The other possibility is that an excessive secretion of CT might be responsible for hypocalcemia, because CT is known to cause hypocalcemia¹³), while increased concentrations of CT in the thyroid gland¹⁴⁻¹⁶) and serum⁷) in patients with PHP type 1 have been reported. However, it has been proposed that hypocalcemia is due to a decreased concentration of $1,25(\text{OH})\text{D}_3$ ¹⁸) which is produced in the kidneys by the action of PTH, and further, a total thyroidectomy fails to improve hypocalcemia in patients with PHP type I¹⁶). This possibility therefore seems unlikely. The reason for the high CT concentration in the present case still remains obscure. One of the possible explanations is the resistance to CT action as described in patients with resistance to other hormones such as TSH, gonadotropins, and ADH, since the adenylate cyclase-cyclic AMP system is known to work as a second messenger for CT action³). Although further studies will be needed to prove this hypothesis, this case might be additional evidence of a generalized defect in the G unit in PHP type 1.

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