Familial Primary Hyperparathyroidism: Study of the Pedigree in Three Generations

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The familial occurrence of primary hyperparathyroidism in which the proband is a 55-year-old man is reported. His 58-year-old sister and 40-year-old brother had undergone partial parathyroidectomy, and histological examination revealed hyperplasia in both cases. Their father and a daughter of the proband had a history of nephrolithiasis. The three siblings showed high levels of plasma parathyroid hormone (even the two postoperative cases). All of them had a history of nephrolithiasis and peptic ulcers. In the proband, image studies did not reveal any abnormality in the neck region. At present, the three cases do not exhibit any abnormalities in the pancreas or the pituitary by imaging studies and endocrine tests. (Internal Medicine 31: 712–715, 1992)

Key words: parathormone, gastrin, MEN type 1

Introduction

The occurrence of familial primary hyperparathyroidism (PHP) is not rare in northern Europe; there are 0.13 cases per 1,000 population (1). In Japan, however, it is very rare with 0.008 to 0.0016 cases per 1,000 population (2); there are few reports on affected families.

Several clinical problems remain unresolved in this familial disorder. The appropriate surgical procedure for parathyroid lesions remains unclear (2); The definition of this disorder in relation to multiple endocrine neoplasia (MEN) type 1 is difficult (2, 3). Management of asymptomatic PHP is also an important clinical issue.

Here we present the clinical course of three typical sibling cases with familial PHP and the family study.

Case Report

The proband was a 55-year-old man, who was admitted to our department in March 1990 with the complaint of insomnia and lumbago. He had suffered from lumbago and urolithiasis since the age of 51. He had a history of fracture of the left hand joint at the age of 34 and partial gastrectomy for a duodenal ulcer at age 44.

On admission, he weighed 73.4 kg, and his height was 165 cm. He was alert and in a good nutritional state. His blood pressure was 128/78 mmHg, and pulse was 60/min

and regular. All his teeth had been replaced with a dental prosthesis and he had oppressive pain in the lumbar region, but otherwise he was physically normal.

Results of laboratory examinations are shown in Tables 1 and 2. The cardinal biochemical and hormonal findings were mild hypercalcemia, hypophosphatemia and high levels of serum alkaline phosphatase and plasma parathyroid hormone (PTH). Urinary output of cyclic AMP and calcium were also high. These findings are compatible with typical PHP. No neck mass lesion including the parathyroid gland was revealed by image studies with CT scanning, echography and scintigraphy by ^{99m}Tc and ^{201}Tl . The negative image study of the neck region may be due to a small parathyroid lesion or ectopic parathyroid (4).

X-ray examinations revealed a small renal stone in the right pelvis and decreased bone density in the lumbar spine, but there was no evidence of osteitis fibrosa cystica. In microdensitometric analysis of the metacarpal bones, definite decreases in the bone mineral content and bone density were shown. The bone mineral content index (ΣGS) was 18.48, lower than the normal average value of $-3.06 \times \text{SD}$, and the bone density index (μ') was 0.429, lower than the normal average value of $-2.76 \times \text{SD}$ (5).

After the examination, we decided against surgical intervention mainly because of a negative image study of the parathyroid lesion. The patient was discharged and is

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Table 1. Routine Laboratory Examinations

1) Blood chemistry		2) Hemogram	
Total protein	6.6 mg/dl	RBC	$431 \times 10^4/\text{mm}^3$
Albumin	4.9 mg/dl	Hb	14.2 g/dl
Total bilirubin	0.8 mg/dl	Ht	41.4%
GOT	22 U/l	Platelet	$20.9 \times 10^4/\text{mm}^3$
GPT	23 U/l	WBC	$6,440/\text{mm}^3$
γ -GTP	27 U/l	(normal differential count)	
Al-P*	207 U/l	3) Urinalysis	
LDH	278 U/l	Protein (-)	
Total cholesterol	206 mg/dl	Glucose (-)	
HDL cholesterol	51 U/l	Sediment: not particular	
Triglycerides	232 mg/dl	4) Feces	
CPK**	58 U/l	Occult blood (-)	
BUN	9.5 mg/dl	5) Arterial gas	
Creatinine	0.8 mg/dl	pH	7.413
Uric acid	7.3 mg/dl	PaO ₂	88.6 mmHg
Fe	161 $\mu\text{g}/\text{dl}$	PaCO ₂	34.9 mmHg
Na	143 mEq/l	Base excess	-1.7
K	4.5 mEq/l	HCO ₃ ⁻	21.0 mEq/l
Cl	110 mEq/l	6) Thyroid functions	
Ca	10.3 mg/dl	TSH	0.86 $\mu\text{U}/\text{l}$
Corrected Ca***	10.8 mg/dl	Free T ₄	1.09 ng/dl
P	1.4 mg/dl		

* Alkaline phosphatase (normal range: 42–123 U/l). ** Creatinine phosphokinase (normal range: 32–166 U/l). *** Corrected Ca = $\text{Ca}/[0.6 + \text{total protein (g/dl)/18.5}]$.

Table 2. Functions Related to Calcium Metabolism

PTH C-terminal*	500 pg/ml (<130)
middle molecule PTH**	2,174 pg/ml (180–560)
Calcitonin	32 pg/ml (15–86)
Urinary Ca output	334.6 mg/day (100–300)
Urinary cyclic AMP	6,249 pmol/ml (2,000–6,000)
% TRP***	69.2% (85–98)
C _{ca} /C _{cr} #	0.018

* Assay kit: "Baxter" ImmunoPTH-C. ** Assay kit: PTH Kit "Yamasa". *** Tubular reabsorption of phosphorus. # Ca clearance/creatinine clearance ratio. Normal ranges in parentheses

now followed asymptotically.

Results of the family study of the proband's paternal side are shown in Fig. 1. The proband's father and one of the proband's daughters had a history of nephrolithiasis, and two of the proband's siblings had a history of parathyroidectomy performed because of PHP. The 58-year-old sister had undergone two operations at the ages of 50 and 52 years and two tumors were resected; it was reported that no other glands were found. The 40-year-old brother had undergone the procedure at the age of 36, with two tumors resected. The histology of the parathyroid gland in both cases was consistent with hyperplasia (Fig. 2).

The brother had a history of total gastrectomy for refractory stomach ulcer at the age of 37, and the sister later suffered from stomach ulcer in 1991. While the brother is now free from symptoms, the sister still suffers from nephrolithiasis with renal stones excreted from the right nephrostoma.

When we examined these two siblings in 1990, corrected serum calcium level was high (10.4 mg/dl) and serum phosphate level was low (1.8 mg/dl) in the sister, but both substances were in the normal ranges in the brother. Plasma PTH levels were still high in both cases; 1,700 and 680 pg/ml, respectively (normal range: 180 to 560 pg/ml as middle molecule PTH using PTH Kit "Yamasa").

In the studies related to MEN syndrome, serum prolactin levels were in the normal range in the three siblings, but serum gastrin levels were high in the sister and the brother (248 and 352 pg/ml, respectively, vs <200 pg/ml for the normal range). The gastrin level in the proband was normal (56 pg/ml). Abdominal and brain CT did not reveal any abnormality in the pancreas or the pituitary in these three cases. In the proband, the results of TRH, LH-RH, insulin loading test, and 75 g-OGTT were within normal ranges (Table 3).

Fig. 1. The pedigree. Squares and circles indicate males and females, respectively. The closed quarter of each square or circle indicates the presence of the indicated characteristics.

Fig. 2. Histologic findings of a parathyroid gland of the sister (A) and the brother (B). Uniform parathyroid cells with acidophilic cytoplasm are shown in both cases (Hematoxylin and eosin, $\times 500$).

Table 3. Pituitary and Pancreas Endocrine Function

1) TRH (500 μ g). LH-RH (100 μ g) and insulin (0.1 μ /kg of body weight)

	0'	30'	60'	90'	120'
Blood glucose (mg/dl)	57	25	48	60	62
Cortisol (μ g/dl)	8.6	9.4	14.6	14.4	13.2
TSH (μ U/ml)	0.90	6.19	4.35	3.13	2.28
PRL (ng/ml)	6.2	31.9	26.8	15.4	10.3
FSH (mIU/ml)	5.2	13.7	14.3	14.1	14.2
LH (mIU/ml)	1.3	22.4	18.8	14.9	12.3
GH (ng/ml)	3.9	5.1	31.8	14.5	6.9

2) 75 g-OGTT

	0'	30'	60'	90'	120'
Blood glucose (mg/dl)	70	150	160	134	104
IRI (μ U/ml)	8.6	65.4	44.4	28.7	17.3
IRG (pg/ml)	70.9	70.5	60.5	55.7	49.3

Discussion

In this family, benign familial hypocalciuric hypercalcemia might have been suspected. However, the high

values of the ratio of calcium clearance to creatinine clearance, and onset of symptoms at a relatively older age are not compatible with this disorder (6). Endocrinologically, plasma PTH levels were clearly elevated in the high sensitivity assay, which is reliable in distinguishing hyperparathyroidism from normal conditions (7).

It has been proposed that surgery for PHP is not indicated when hypercalcemia is not marked (<12 mg/dl) an bone change has not progressed to osteitis fibrosa cystica; even if silent renal impairment is present, surgical treatment for PHP is not always appropriate (8). In the present case, we also avoided surgical treatment for the proband because of a negative image study of the lesion and due to the reported high recurrence rates after surgery (9). However, as it is also reported that the involvement of renal or skeletal systems are an indication for surgery (10), the proband should be followed conscientiously as a possible subject for surgical treatment.

The proband's sister and brother had each undergone an operation in which two glands were resected. Both patients, however, showed high levels of plasma PTH after the operation, and the sister still suffered from nephrolithiasis. These facts suggest that partial parathyroidectomy as performed in these cases might not be an appropriate procedure, especially in familial PHP. Some researchers strongly emphasize the necessity for subtotal parathyroidectomy in familial PHP (2, 11). Factors likely to optimize the outcome in this group are reported to include preoperative recognition of the specific hereditary disorder, involvement of experienced surgeons, and efforts to identify histologically four or more parathyroid glands (9).

In this report, we examined the familial occurrence of PHP in three generations, including the typical cases of the three siblings and the proband's daughter and father as possible cases. Familial PHP is described as a partial symptom of MEN type 1 (2, 11), with an occurrence of approximately 97% of PHP in MEN type 1 (12). The histology of the parathyroid lesion in MEN type 1 is usually hyperplasia (2), which is compatible with our operated cases. Although we have not yet obtained evidence for pituitary or pancreas lesions in these cases, we think it is quite possible that this family may develop MEN in the future. We are following the family in this context.

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