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NOTE

Clinical and Biochemical Presentation of Primary Hyperparathyroidism in Kansai District of Japan

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Abstract. Although the number of patients with primary hyperparathyroidism (pHPT) has increased since biochemical screening came to be widely employed, few data are available concerning the clinical analysis of Japanese patients. We therefore tried to determine the recent clinical and biochemical state of Japanese patients with pHPT. Clinical and biochemical data were analyzed in a series of 103 pHPT patients who had been hospitalized in Kobe University Hospital during a 17 year period from 1979 to 1995. The data were obtained from the hospital records and additionally from information through questionnaires performed in 1995. Patients were 29 males and 74 females. The average ages at diagnosis were 53.4 ± 16.0 (SD) year-old and 53.9 ± 15.2 year-old, respectively. The major clinical symptoms were nephrolithiasis (35.9%), thirst/polyuria (33.0%), easy fatigability (20.4%) and back pain/lumbago (16.5%), but 19.4% of the patients were asymptomatic. Out of 87 cases who received parathyroidectomy, 10 (11.5%) were diagnosed with parathyroid carcinoma. Age- and sex- corrected bone mineral density (BMD) of the radius was significantly lower in the group with back pain/lumbago than in the group without the symptom. Similarly, radial BMD was lower in the group with a high serum alkaline phosphatase value. Patients with nephrolithiasis had a lower urinary calcium/creatinine ratio (UCa/UCr; 0.305 ± 0.188 mg/mg) than the patients without nephrolithiasis (0.400 ± 0.160 mg/mg). This inconsistent result suggests that some important factors except urinary calcium would contribute to urinary stone formation in pHPT. Our data mostly agreed with previous reports on a Caucasian population except for a relatively high prevalence of parathyroid carcinoma, but the negative correlation between nephrolithiasis and urinary calcium was not easily explicable. This finding should be confirmed by analyzing a larger number of cases.

Key words: Primary hyperparathyroidism, Nephrolithiasis, Bone mineral density, Urinary calcium, Japanese

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PRIMARY hyperparathyroidism (pHPT) has become a common endocrine disorder since the multi-channel autoanalyzer was introduced for biochemical examinations. A recent epidemiologic review in Sweden [1] reported that more than 1% of all postmenopausal females could be diagnosed as having pHPT. The prevalence of pHPT mentioned in another review paper was about 1300 per million in various clinical series and 4276 per million in Stockholm [2]. The clinical features of pHPT had been well described, but the increasing number of patients incidentally discovered by routine biochemical screening has changed the clinical presentation of pHPT to a milder one. Although pHPT is identified with increasing frequency, few data are available concerning the clinical analysis of this condition in Japan.

In this paper we will describe the clinical and biochemical features of pHPT by analyzing a series of 103 Japanese patients hospitalized in Kobe University Hospital during the past 17 years.

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Materials and Methods

We studied 103 Japanese patients diagnosed as pHPT who had been hospitalized in Kobe University Hospital during a 17 year period from 1979 to 1995. The clinical and biochemical data were obtained by reviewing the chart records at the first admission. The laboratory data were assayed at the central laboratory of Kobe University Hospital. Parathyroid hormone (PTH) was determined by radioimmunoassay (RIA) and Imuunoradiometric assay (IRMA) measuring either or both C-terminal (Eiken PTH assay kit; Eiken Co., Tokyo, Japan), intact (1–84) (PTH Intact Allegro; Nichols Institute, San Juan, CA, USA), and/or mid-portion (44–68) PTH (Hypersensitive PTH; Yamasa Shoyu Co., Chiba, Japan). The biochemical data were chosen from multiple measurements to represent each of the conditions. Urinary calcium and phosphorus were measured from 24-h urine specimens acidified with HCl. Bone mineral density (BMD) at one third of the radius was measured by single photon absorptiometry (Bone Mineral Analyzer 278O, Norland Co. WI, USA), and BMD of the lumbar spine was measured by dual energy X-ray absortiometry (QDR-1000, Hologic Inc. MA, USA). An age- and sex-corrected parameter of BMD, the Z score was expressed as standard deviation of average BMD at each age. The pathological diagnoses were confirmed by the reports authorized by pathologists. As for histories of the disease and other coexisisting diseases, we also tried to obtain information directly from the patients by mail in June, 1995 to complement the data. Patients suspected of having familial hypocalciuric hypercalcemia, multiple endocrine adenomas or any conditions indistinguishable from tertiary hyperparathyroidism were excluded from the study group.

The statistical analysis was performed with StatView 4.0 computer software (Abacus Concepts Inc.). Differences between groups were compared by ANOVA.

Table 1. Symptoms and complications associated with primary parathyroidism

Symptoms and complications	Number (%) of cases
Nephrolithiasis	37 (35.9)
Thirst / Polyuria	34 (33.0)
Easy fatigability	21 (20.4)
Back pain/Lumbago	18 (17.5)
Weight loss	8 (7.8)
Insomnia/Irritability	2 (1.9)
Numbness of the extremities	2 (1.9)
Constipation	1 (1.0)
Asymptomatic	20 (19.4)

Results

The study group comprised 74 women and 29 men with a female : male ratio of 2.55 : 1. The mean age at diagnosis of pHPT was 53.8 ± 15.3 (range 16–82) years old for the total population, 53.9 ± 15.2 (range 16–80) years old for women and 53.4 ± 16.0 (range 20–82) years old for men. The age at diagnosis peaked in the sixth decade (37.8%), but 11 patients (10.6%) were diagnosed before the age of 30.

Based on the hypothesis that some genetic factors may be associated with the tumorgenesis of the parathyroid glands, we examined for the presence or absence of a family history of malignancy related to the age at diagnosis. The mean age at diagnosis of the patients who had one or more relatives within the third degree with malignant disease was 50.1 ± 16.7 years old for women (n=37) and 53.7 ± 15.4 years old for men (n=14), while patients who did not have a family history of malignancy were 57.9 ± 12.6 years old (n=37) and 53.1 ± 17.0 years old (n=15), respectively. Although there was no statistical significance, the patients with a family history of malignancy were likely to be diagnosed somewhat earlier in the female group. Out of 11 cases (8 women and 3 men) who were diagnosed before the age of 30, 8 patients (7 women and 1 man) had a family history of malignancy.

The symptoms and complications associated with pHPT are listed in Table 1. Out of 103 patients, nephrolithiasis (including calcification of the renal parenchyma) was the most frequent. Thirst/polyuria was the second. Complaints of easy fatigability and back pain/lumbago were not specific to pHPT, but they were often relieved after surgical treatment. In the two patients who complained of irritability and insomnia, the symptoms were diminished after surgery. Asymptomatic patients were 19.4%.

As for accompanying diseases, thyroid diseases

were found in 49 patients (41 women and 8 men), that is, thyroid diseases were found in 47.6% of pHPT patients, in 55.4% in the female group and in 27.6% in the male group. Among the patients with thyroid diseases, 12 patients (24.5%) had thyroid carcinomas. The other coexisting diseases were as follows: hypertension (24.2%), appendicitis (10.7%), cholelithiasis (10.7%), peptic ulcer (8.7%), cerebrovascular accident (5.8%), diabetes mellitus (5.8%), hyperlipidemia (4.9%), etc. Malignant diseases excluding thyroid carcinoma were found in six patients (multiple myeloma in two patients and gastric, breast, esophageal and uterine cancer in one, respectively). Because one patient had both thyroid and gastric cancer, there were 17 malignancies (16.5%).

Surgical treatment was performed in 87 patients. Parathyroidectomy was not performed when the disease was mild, when the tumor responsible could not be identified or when the patient did not consent to surgery. Out of 87 cases, 10 (11.5% of the group operated on, 9.7% of the total) were diagnosed as carcinoma and three as hyperplasia of multiple glands. Eighty-six cases out of 103 were suspected of having single gland abnormality. The affected sites were the left inferior gland in 33 cases (40.0%), the right inferior gland in 27 cases (32.5%), the left superior gland in 10 cases (12.0%) and the right superior gland in 7 cases (8.4%). Three arose in the right-sided glands but the origin was unable to be determined. Similarly, two were on the left but it was not clear in which glands they originated. Three others arose in the mediastinum and one in the thyroid. Out of 10 carcinomas, five arose in the right inferior gland and two in the left inferior gland. The other three were in the right superior gland, in the undetermined right-sided gland and in the undetermined left-sided gland.

The mean serum calcium value before surgery was 11.33 ± 1.21 mg/dL. The calcium level was 12.10 ± 1.60 mg/dL in the cancer cases and 11.37 ± 1.18 mg/dL in the non-cancer cases. On the other hand, the mean serum phosphorus value was 2.49 ± 0.51 mg/dL in total, 2.45 ± 0.59 mg/dL in cancer cases and 2.49 ± 0.51 mg/dL in non-cancer cases. The mean calcium value tended to be higher and phosphorus values to be lower in the cancer cases, but they were not statistically significant. Because thirst and polyuria are often associated with a high serum calcium concentration, we examined if the symptoms had any relation to the serum calcium level. The mean serum calcium value was 11.54 ± 1.38 mg/dl in the group with thirst/polyuria (n=33) and 11.22 ± 1.11 mg/dL in the group without the symptoms (n=70). There was therefore no significant correlation.

The serum alkaline phosphatase (ALP) values were compared by calculating the ratio to the value of the normal limit for each assay method because the assay method employed at the laboratory had changed several times during the study period. Out of 100 cases in which ALP values were available, the ALP value exceeded the normal limit in 70 cases, and was more than double the normal limit in 23 cases. In the cancer group, 6 out of 10 cases (60.0%) had an higher ALP value more than double the normal limit, whereas only 13 out of 74 cases (17.6%) in the non-cancer group had an ALP value more than double the normal limit. In the 16 non-operated cases, only two exceeded double the normal limit.

Nephrolithiasis was the most frequent complication in this study. Stone formation in the urinary tract was reported to be associated with the amount of calcium excretion in pHPT patients [3]. We therefore examined the urinary calcium to creatinine ratio (UCa/UCr) and calcium clearance to creatinine clearance ratio (CCa/CCr) to see the association between nephrolithiasis and urinary calcium excretion. The biochemical differences between the two groups with and without nephrolithiasis are summarized in Table 2. Interestingly, the mean UCa/UCr was significantly lower in the group with nephrolithiasis than in the group without nephrolithiasis. The CCa/CCr ratio also showed a similar significant difference between the two groups. As for the correlation between urinary phosphorus and the presence or absence of nephrolithiasis, we examined the tubular maximal reabsorption of phosphate/GFR (TmP/GFR) as an index of urinary phosphorus reabsorption, but the mean TmP/GFR values for the two groups were not significantly different.

The BMD values for the radius and the lumbar spine in the study group were reduced for Z scores of −2.13 ± 2.41 and −0.83 ± 1.16, respectively. The Z score for the radius (reflecting the status of cortical bone) was −3.51 ± 3.11 (n=16) in the patients with back pain/lumbago and −1.81 ± 2.12 (n=68) in those without the symptom. Thus, lumbago/back pain was significantly associated

Table 2. Biochemical data of the groups with or without nephrolithiasis

	nephrolithiasis (+)	nephrolithasis (–)	total
s-Ca (mg/dL)	11.17 ± 1.17 (n=37)	11.41 ± 1.23 (n=66)	11.33 ± 1.21 (n=103)
s-P (mg/dL)	2.46 ± 0.44 (n=37)	2.51 ± 0.55 (n=66)	2.49 ± 0.51 (m=103)
C-PTH (pg/mL)	1562 ± 1327 (n=13)	1320 ± 1140 (n=16)	1428 ± 1211 (n=29)
intact PTH (pg/mL)	226.1 ± 263.4 (n=17)	208.2 ± 250.3 (n=39)	213.6 ± 252.1 (n=56)
mid PTH (pg/mL)	2660 ± 3320 (n=23)	2274 ± 2142 (n=46)	2403 ± 2572 (n=69)
UCa/UCr (mg/mg)	0.30 ± 0.19 * (n=37)	0.40 ± 0.16 (n=65)	0.37 ± 0.18 (n=102)
CCa/CCr	0.023 ± 0.011 * (n=36)	0.028 ± 0.013 (n=64)	0.026 ± 0.012 (n=100)
TmPO4/GFR (mg/100mL)	2.02 ± 0.64 (n=37)	2.03 ± 0.69 (n=66)	2.03 ± 0.67 (n=103)

Normal range: s-Ca 8.4–9.9; s-P 2.4–4.5; C-PTH <600; intact PTH 15–50; mid PTH 160–520; UCa/UCr <0.2; CCa/CCr >0.01 (in hypercalcemic state); TmPO4/GFR 2.3–4.3. *P<0.05 by Fisher's PLSD test: *vs.* nephrolithiasis (–).

with lower radial BMD (P<0.05). On the other hand, the difference of the Z scores for the lumbar BMD (reflecting the status of cancellous bone) was not obvious; −1.33 ± 1.37 (n=6) in the patients with back pain/lumbago and −0.73 ± 1.12 (n=31) in those without the symptom. The Z score for the radial BMD was lower in the patients whose serum ALP values were higher than double the normal limit than in those whose ALP values were within double the normal limit; −4.46 ± 2.23 (n=20) *vs.* −1.14 ± 1.98 (n=64), respecitvely (P<0.05). The frequency of the patients whose serum ALP values were higher than double the normal limit was significantly higher in the patients with back pain/lumbago (47.1%) than in those without the symptom (19.5%) (P<0.01). BMD was not significantly different in the two groups with nephrolithiasis and without nephrolithiasis (data not shown).

Discussion

As more insidious cases of pHPT have been disclosed by biochemical screening, the clinical presentation of pHPT has been changing. This study describes the clinical picture of 103 patients with pHPT who had been hospitalized in Kobe University Hospital from 1979 to 1995. During that period, the multi-channel autoanalyzer was already in clinical use. The study group comprised 74 women and 29 men with a female : male ratio of 2.55 : 1, which generally agreed with the previous reports [4]. The age at diagnosis peaked in the sixth decade as in other reports [4, 5], but 10.6% of the patients were diagnosed before the age of 30, which caused us to consider the relationship between the age at diagnosis and the family history of malignancy as a background factor. Although there was no statistical significance, we found evidence that the patients who had a family history of malignancy were likely to be found at a relatively younger age in women. This tendency was not seen in men. It is not sure whether this tendency is a universal finding or not because there is no previous report describing this relationship, but the present findings suggest that some genetic factors may contribute to the pathogenesis of pHPT.

The most frequent condition associated with pHPT was nephrolithiasis at 35.9%, which is generally compatible with previous reports [4, 6], but the frequency of nephrolithiasis has been significantly lower in reports published since 1985 (18 to 28%) than in those before 1970 (40 to 68%)

[7]. This change presumably reflects the improvement in the detecting threshold for pHPT due to the introduction of the multi-channel autoanalyzer. Since the patients in our study group were all diagnosed after the introduction of the multi-channel autoanalyzer, the frequency of nephrolithiasis in the study group seems to be high. One reason for the difference may be that we included the cases with small calcified lesions in the kidneys, whose condition was clinically silent. There were 19.4% of asymptomatic patients, but smaller and more non-specific symptoms such as easy fatigability are likely to be overlooked in history-taking. However, these symptoms should be considered when choosing medical or surgical treatment because they are often relieved by surgery. A series of studies that investigated neuropsychological problems before and after surgery suggested an association between pHPT and neuropsychological symptoms [8, 9], though the findings are not generally accepted [10, 11]. It seems to be important to determine whether the symptoms are associated with the condition brought on by pHPT.

Thyroid diseases were found in 49 patients (47.6%) and carcinoma was found in 12 (11.7%). Because the thyroid carcinomas were all found incidentally during the examination for pHPT or during the surgery, the frequency was regarded as a chance association. It is therefore unclear whether pHPT is likely to accompany thyroid disease or not. According to Attie and Vardham, 26% of operated pHPT had thyroid lesions, and 31 out of 948 cases (3.3%) were found to have thyroid carcinomas [12]. The frequency of thyroid diseases was lower than in our cases, but considering that the thyroid lesions were basically latent in the study group, the difference in the prevalence of thyroid lesions may reflect the progress in diagnostic methods, especially in imaging technology.

Among pHPT with a single gland parathyroid tumor, 72.5% arose in the inferior glands in this study. There are few recent reports mentioning the localization of parathyroid tumors except for a textbook describing that parathyroid adenomas seemed to develop at similar frequency in all four parathyroid glands [13], but classical cases were reported to have a slight predominance of parathyroid adenomas of the right inferior gland [14]. In a recent paper concerning the radio-nuclide imaging of parathyroid glands, 15 out of 19 parathyroid tumors were reported to originate in the inferior glands in patients with pHPT in Canada [15]. Among the operated group, 11.5% were diagnosed as carcinoma. In contrast to previous reports stating that parathyroid carcinoma was found in only 0.3–3.0% of pHPT cases in a Caucasian population [16–19], our study revealed a very high incidence of parathyroid carcinoma in Japanese patients. Obara and Fujimoto also reported that parathyroid carcinoma was more common in Japanese patients with pHPT [19]. They found parathyroid carcinoma in 4.6% of patients with pHPT. Fifty persent of the parathyroid carcinomas originated in the right inferior gland, that is, 18.5% of the parathyroid tumors of the right inferior gland were malignant. In this study, 7 out of 10 carcinomas were right-sided and the other three were left-sided. The number of cases with parathyroid carcinoma was so small that we cannot tell if carcinomas tend to originate in the right.

The unexpected result respecting the association between the urinary calcium concentration and nephrolithiasis would suggest that stone formation is not directly linked to the urinary calcium level. Mallette and his colleagues reported that patients with nephrolithiasis tended to have moderate hypercalcemia, a longer duration of symptoms and perhaps slowly growing tumors [14]. Assuming that a long period of disease is important in stone formation, patients with relatively low urinary calcium excretion may have a long history of the disease because of milder abnormalities. On the other hand, patients with a higher urinary calcium concentration may tend to be detected in the earlier stage of the disease, probably before stones are formed. There are some other factors associated with stone formation. Pak and Holt reported that the urine of patients with hyperparathyroidism was significantly more supersaturated with calcium oxalate and brushite [20]. These stone forming constituents may increase the propensity for crystallization of stone forming calcium salts, whereas pyrophosphate, citrate and magnesium are known as inhibitors of crystallization of calcium salts. Most pHPT stone formers produced stones composed mainly of calcium phosphate and calcium oxalate [7]. Because high urine pH is known to promote calcium phosphate crystallization [21], urine pH would also be important for stone formation in pHPT because reabsorption of urinary HCO_3^- is reduced

according to the PTH action on the proximal renal tubules. Alvarez-Arroyo and his colleagues reported that stone formers in pHPT patients had lower urinary citrate excretion than patients without stones, due to increased tubular reabsorption of citrate [22]. We could not obtain the data concerning these factors contributing to stone formation. It is therefore unclear whether a relatively low urinary calcium concentration may play a causative role in stone formation. This negative correlation between urinary calcium and nephrolithaisis makes us think that there may be a somewhat special pathogenesis of nephrolithiasis in pHPT patients.

The radial bone BMD at the distal one third site was reduced in the study group, but the lumbar bone density was relatively well preserved. This was consistent with reports mentioning that cortical bone was dominantly affected in pHPT [23, 24]. An association between ALP and low BMD was also confirmed in the study as previously reported [24]. We found interesting associations between back pain/lumbago and radial BMD as well as ALP. Back pain and lumbago are often caused by disorders of ligaments and muscles. In addition, the lumbar bone density was relatively well preserved and the difference in the lumbar BMD was not obvious in the groups with and without back pain/lumbago. Nevertheless, the present data suggest that the symptom of back pain or lumbago should be still estimated as a sign of skeletal affection in pHPT.

The clinical presentation of pHPT is still changing as the frequency of incidental discovery of hypercalcemia by biochemical mass screening increases. Because of the latency and the high prevalence of the disease, the management of pHPT patients would also be important as a public health problem. In this paper, we have described an update of pHPT in Japanese patients. Comparing our results with previous reports on Caucasian populations, our study group showed a higher prevalence of parathyroid carcinoma and coexisting thyroid cancer. It is unclear at present whether they reflect the racial difference or some difference in diagnostic processes. Because the findings in this study were obtained by retrospective analyses, further prospective studies are necessary to reach firm conclusions. To get a complete picture of pHPT, longitudinal and demographic studies on a large scale in each region of the world would be important.

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