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ORIGINAL ARTICLE

Primary hyperparathyroidism in Taiwan: clinical features and prevalence in a single-center experience

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Abstract In Taiwan, urolithiasis remains a common manifestation of primary hyperparathyroidism (PHPT). We designed this study to estimate the prevalence of PHPT in asymptomatic adults and to assess the complications already present when the disease was diagnosed. In the first phase of the study, we retrospectively reviewed 50 patients diagnosed with surgically or biochemically proven PHPT between April 1995 and April 2007. In the second phase, we reviewed the records of 4,359 asymptomatic subjects who had undergone a health examination between August 2002 and January 2007. Of the 50 patients reviewed in the first phase, hypercalcemia was the presenting complication in 33 patients (64%) followed by symptomatic recurrent solitary urolithiasis in 10 patients (20%). Of the 43 patients who underwent urologic imaging, 29 (67%) had urolithiasis and 7 (16%) had nephrocalcinosis, indicating that urinary stone disease is common. In the second phase, 28 of the 4,359 asymptomatic adults (0.64%) were found to have hypercalcemia; of these 28, 4 (0.092%) were diagnosed with PHPT. In Taiwan, PHPT remains underdiagnosed, and complications manifest in most patients upon admission. Although still relatively uncommon, screening serum calcium levels helps diagnose PHPT at an asymptomatic stage.

Keywords Primary hyperparathyroidism · Urolithiasis · Prevalence

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Introduction

In the past, primary hyperparathyroidism (PHPT) was described as a disease of "bones, stones, and groans" because it often presented with osteoporotic fractures or urinary calculi. Other manifestations included hypercalcemic crisis, hypertension, mental disorders, and peptic ulcer disease [1–3]. As routine biochemical blood tests became more popular in the West in the 1970s, an increasing number of patients were diagnosed with PHPT even when they were in the asymptomatic phase of the disease. For example, the apparent incidence of PHPT at the Mayo Clinic increased from 7.8 cases per 100,000 between 1965 and 1974 to 51.1 cases per 100,000 in 1976. In the earlier period, only 18% of the patients were asymptomatic when diagnosed as compared to 51% in the final 2 years [4]. Urolithiasis was present in around 50% of the patients in the earlier period, but in only 4% of the patients in the later period. It has been estimated more recently that only about 20% of the patients diagnosed with PHPT in the West have urolithiasis [4–6]. This is in contrast with a report from China by Bilezikian et al., noting a 42% prevalence of urolithiasis in Chinese women diagnosed with PHPT [7]. We speculated that the findings would be similar in

Taiwan, as serum calcium levels are usually not measured routinely. Therefore, we designed this two-part retrospective, hospital-based study to assess the presentation of PHPT, particularly the incidence of urolithiasis, and to calculate the incidence of asymptomatic PHPT in individuals who have undergone biochemical screening.

Materials and methods

In order to obtain an adequate sample, a retrospective review of hospital charts covering a 12-year period, from April 1995 to April 2007, was performed. Of 550,000 admission records containing the diagnosis of hyperparathyroidism, hypercalcemia, or parathyroidectomy, 237 were retrieved for review. Patients with secondary hyperparathyroidism or other causes of hypercalcemia, such as malignancy, immobility, vitamin D intoxication, or milk-alkali syndrome, were excluded, leaving 50 patients with biochemically, image-, or surgically proven PHPT. Data extracted from the records included clinical details such as biochemistry data [total calcium, phosphate, creatinine, and intact parathyroid hormone (i-PTH) levels] and data from imaging studies (parathyroid technetium-sestamibi scan, neck ultrasonography, intravenous pyelography, and kidney ultrasonography) and treatment. Kidney ultrasonography was performed by experienced urologists or nephrologists. Urolithiasis was diagnosed in the presence of stones on kidney ultrasonography, X-ray films, or intravenous pyelography. Nephrocalcinosis was diagnosed if diffuse renal parenchymal calcification was seen on ultrasonography.

The second phase of the study was based on records of health maintenance examinations performed at the Mackay Memorial Hospital between August 2002 and January 2007. The subjects were healthy individuals including office workers, laborers, students, retirees, housekeepers, etc., and were not restricted by age, sex, occupation, or socioeconomic status. The serum calcium, phosphate, and albumin levels were measured routinely as part of the examination. Of the 4359 people examined in that period, we evaluated all those with hypercalcemia ($Ca^{2+} > 10.3$ mg/dl corrected for serum albumin). Statistical analysis was performed with Statistical Package of Social Science software (SPSS 11.0, 2001; SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± SEM unless otherwise stated. Student's *t* test or χ^2 analysis was used for between-group comparisons. A P value <0.05 was considered statistically significant.

Results

The age of the 50 patients diagnosed with PHPT in the first phase of the study ranged from 18 to 89 years (mean: 60.7 ± 2.4 years). Basic demographics revealed that PHPT predominantly occurred in women over 60 years of age (Table 1). The elevated i-PTH and total calcium levels along with decreased serum phosphate levels were compatible with PHPT. Secondary hyperparathyroidism was excluded; the patients had a mean serum creatinine level of 1.45 ± 0.16 mg/dl. Of the 50 patients, diagnosis of PHPT was first suspected in 32 patients (64%) because of unexpected hypercalcemia detected by biochemical screening, in 10 (20%) because of recurrent solitary urolithiasis and in 5 (10%) because of a neck mass (Table 1). Five patients had hypercalcemic crisis ($Ca^{2+} > 15$ mg/dl) and one had acute pancreatitis. Although urolithiasis was not the presenting complaint in majority of the patients, 43 were investigated for this complication, of whom 29 had stones and 7 had nephrocalcinosis. Treatment included parathyroidectomy, percutaneous ethanol injection therapy (PEIT), and conservative medical treatment. Hypercalcemia is the most common indication for treatment (Table 1). Chronological analysis was performed, and there was no difference between the first half (1995–2001) and the last half (2002–2007) (Table 2).

In the second phase of the study, data were collected on 4,359 people whose ages ranged from 21 to 94 years (mean: 52.3 ± 0.2 years) (Table 3). In the second phase of these 4,359, 28 (0.64%) had hypercalcemia. The age of these 28 ranged from 47 to 76 years (mean: 54.9 ± 2 years). Their mean serum calcium level (corrected for serum albumin) was 10.65 ± 0.13 mg/dl and alkaline phosphatase level was 129.6 IU/l ± 38.5 (Table 4). No definitive diagnosis was made in 14 of these patients as they were lost to follow-up. Of the remaining 14, 7 had hyperthyroidism, 4 had PHPT, and 2 had normal serum calcium levels in the following examination. The prevalence of PHPT in this group of 4,359 asymptomatic adults was 0.092% (Table 4). Of the four patients with PHPT, three were women, and the age range of the 4 (47 to 76 years) was similar to that in the first phase of our study.

Discussion

This report presents both the clinical manifestations and the incidence of PHPT in asymptomatic individuals in Taiwan. PHPT is an underdiagnosed condition, and it can be diagnosed early by screening the serum calcium levels.

In the present study, although PHPT was found to be more prevalent in women (31 of 50), the female-to-male ratio (1.63) is somewhat different from that found in other large series conducted in Western [2, 5, 8] or Eastern countries [9, 10]. However, in one series conducted in Hong Kong, the female-to-male ratio was determined to be 1.98, which is similar to our findings [11]. This likeness

Table 1 Demographics, biochemical data, and presenting problems in a hospital-based study of 50 patients diagnosed with primary hyperparathyroidism in Taiwan, 1995–2007

Demographics	Mean ± SEM	Median (IQR)
Age (years)	60.7 ± 2.4	62.5 (27)
≥60	32	
<60, ≥40	10	
<40	8	
Men/women	19/31	
Biochemistry data		
Calcium (8.9–10.3 mg/dl)	11.95 ± 0.31	11.6 (1)
Phosphate (2.7–4.5 mg/dl)	2.83 ± 0.12	2.7 (1)
Creatinine (0.4–1.2 mg/dl)	1.45 ± 0.16	1.15 (1)
i-PTH (12–72 pg/ml)	444.8 ± 75.4	256 (469)
Urine calcium excretion (mg/24 h)	290.3 ± 47.7	265 (327)
Clinical manifestations	**No. of patients ($n = 50$)**	**Percentage**
Positive of imaging findings		
Parathyroid technetium-sestamibi scan	33/43	76.74
Neck ultrasonography	20/25	80
Positive of osteoporosis	7/14	50
Indication for testing		
Hypercalcemia	33	66
Urolithiasis	10	20
Neck mass	5	10
Other	2	4
Treatment modality		
Parathyroidectomy	26	52
PEIT	8	16
Medical treatment	16	32

i-PTH intact parathyroid hormone, *PEIT* percutaneous ethanol injection therapy

Table 2 Chronological analysis in a hospital-based study of 50 patients diagnosed with primary hyperparathyroidism in Taiwan, 1995–2007

Demographics	1995–2001 ($n = 16$)	2002–2007 ($n = 34$)	P value
Age (years)	59.31 ± 4	61.35 ± 3.03	0.969
≥60	8	24	0.121
<60, ≥40	6	4	0.121
<40	2	6	0.121
Men/women	8/8	11/23	0.349
Biochemistry data			
Calcium (8.9–10.3 mg/dl)	12.22 ± 0.57	11.78 ± 0.33	0.477
Phosphate (2.7–4.5 mg/dl)	2.82 ± 0.21	2.82 ± 0.14	0.996
Creatinine (0.4–1.2 mg/dl)	2.06 ± 0.39	1.23 ± 0.12	0.077
i-PTH (12–72 pg/ml)	354.08 ± 74.25	510.78 ± 96.55	0.385
Urine calcium excretion (mg/24 h)	235.65 ± 26.41	308.39 ± 39.08	0.547

i-PTH intact parathyroid hormone

Data are expressed as mean ± SEM unless otherwise stated

could be attributed to the racial similarity of Hong Kong and Taiwan residents, who are of Chinese origin, thus indicating that this disease may have a racial predilection. However, a large-scale prevalence study is crucial to confirm this hypothesis.

Urolithiasis and nephrocalcinosis are the common presentations of PHPT. Risk factors include hypercalciuria, hyperoxaluria, low urinary citrate concentration, and alkaline urine [12–14]. In our series, urolithiasis or nephrocalcinosis was present in at least 72% of our patients.

Table 3 Demographic and biochemical data for 4,359 healthy adults evaluated in a routine health examination in Taiwan, 2002–2007

Demographics	Mean ± SEM	Median (IQR)
Age (years)	52.27 ± 0.2	52 (16)
Men/women	2315/2044	
Biochemistry data		
Calcium before correction (8.9–10.3 mg/dl)	9.26 ± 0.01	9.3 (0.7)
Calcium after correction (8.9–10.3 mg/dl)	9.02 ± 0.01	8.98 (0.64)
Albumin (3.5–5.0 g/dl)	4.5 ± 0.00	4.5 (0.4)
Phosphate (2.7–4.5 mg/dl)	3.6 ± 0.01	3.6 (0.7)
Alk-P (38–126 IU/l)	69.4 ± 0.4	66 (24)
Creatinine (0.4–1.2 mg/dl)	0.92 ± 0.01	0.9 (0.3)
	No. of patients (n = 4359)	Percentage
Hypercalcemia subjects	28	0.64

Alk-P alkaline phosphate

Table 4 Demographics and biochemistry data of 28 patients with hypercalcemia identified on a health screening examination in Taiwan, 2002–2007

Demographics	Mean ± SEM	Median (IQR)
Age (year)	54.86 ± 2	57 (15)
Men/women	9/19	
Biochemistry data		
Calcium before correction (8.9–10.3 mg/dl)	10.65 ± 0.13	10.6 (0.4)
Calcium after correction (8.9–10.3 mg/dl)	10.65 ± 0.13	10.44 (0.2)
Albumin (3.5–5.0 g/dl)	4.17 ± 0.03	4.2 (0.5)
Phosphate (2.7–4.5 mg/dl)	3.95 ± 0.17	4.15 (1.5)
Alk-P (38–126 IU/l)	129.6 ± 38.5	89 (76)
Creatinine (0.4–1.2 mg/dl)	0.89 ± 0.05	0.8 (0.3)
Diagnosis, number (%)	No of patients (n = 4359)	Percentage
Primary hyperparathyroidism	4	0.092
Hyperthyroidism	7	0.161
Granulomatous disease	1	0.002
Malignency	0	0
Transient hypercalcemia	2	0.046
Unrecognized	14	0.321

Alk-P alkaline phosphate

Data are expressed as mean ± SEM unless otherwise stated

The incidence of urolithiasis or nephrocalcinosis in our study was much higher than the 20 and 42% reported in studies conducted in Western countries and mainland China, respectively [7]. Nephrocalcinosis is a term used to describe diffuse spotty calcification of the renal parenchyma, as seen radiographically, and it is thought to be more common in non-PTH-mediated hypercalcemia than in PHPT [15, 16]. This condition was detected in 7 of the 43 patients (16.3%) who underwent image investigation in our series. This was higher than the 3.6% reported by Peacock [15] in USA, but similar to the 12.8% reported in India [17]. It is possible that PHPT in Chinese patients in Taiwan simply causes more urolithiasis and nephrocalcinosis than it does elsewhere, but this is unlikely because of the lower prevalence in China. Alternatively, it is possible that PHPT is more underdiagnosed in Taiwan than in other countries, such that when it is finally recognized, many of the patients have already developed the adverse renal effects of long-term hypercalciuria. This explains why nearly three-quarters of our patients had clinical

manifestations and much higher serum i-PTH levels when they were diagnosed. On the other hand, it is also possible that these hospitalized patients were sicker than those with milder symptoms who were diagnosed in the outpatient department. However, 33 of the 50 patients in the first phase of the study were diagnosed incidentally when hypercalcemia was detected during their hospitalization (many more patients were not screened for hypercalcemia), and 14 of 28 hypercalcemic patients in the second phase of the study were lost to follow-up after the health examination. This suggests that recognition of PHPT as the potential cause of hypercalcemia is underestimated. Therefore, we suspect that PHPT is not diagnosed in many asymptomatic and even some symptomatic patients because the disease is not considered common in Taiwan.

Routine measurement of serum calcium levels reportedly detects at least 250 new cases of PHPT per million per year in Western countries [2, 5]. The second phase study group included individuals from a wide range of age and socioeconomic status to represent the general population in Taiwan. Four of more than 4,000 asymptomatic individuals were diagnosed with PHPT, representing a minimum estimated prevalence of 92 per 100,000 or an annual incidence of approximately 17.5 per 100,000. This compares, for example, with an annual incidence of 20.8 per 100,000 reported in Minnesota [8]. However, 14 of 28 hypercalcemic patients were lost to follow-up, and the causes of hypercalcemia were not recognized. Assuming none of the 14 patients had a definite diagnosis of PHPT, the prevalence of PHPT in this group of 4,359 asymptomatic adults was 0.092% (Table 4). If the prevalence among 14 patients who were not investigated was the same, then the total prevalence would be 0.18%. This suggests that routine measurement of serum calcium levels alone is not sufficient and that it needs to be properly evaluated afterward. There may not be much of a difference between the prevalence of PHPT in Eastern and Western countries, but population-based studies should be undertaken in non-Western countries to assess the true prevalence of this disease. Routine screening in patients with urolithiasis for parathyroid disease is not recommended by the authors of these studies because the incidence of PHPT is low in the West (only 2% in a Belgian study regarding 1433 patients with stones) [18, 19]. There are no comparable Asian studies on the incidence of PHPT in patients with urolithiasis. Until such data are available, we recommend that measuring serum calcium levels is warranted in patients with urolithiasis or nephrocalcinosis in Taiwan, particularly in those with recurrent stone formation.

Parathyroidectomy is the treatment for symptomatic PHPT and is curative if successful [20, 21]. In our hospital, we follow the National Institutes of Health 1991 guidelines for recommending surgery [22]. The presentations of 11 patients in our series matched the guideline criteria for recommending parathyroidectomy, but they were treated conservatively. Surgery may have been refused because patients thought that the risk was unacceptable, or they may have had underlying comorbidity that precluded an operation. Sixteen patients received medical treatment including bisphosphonate, calcitonin, and calcimimetics. A higher rate of parathyroidectomy (52%) was noted in the first phase of our study; this is not surprising since most of our patients were symptomatic. Among the patients who were treated with PEIT, the serum levels of i-PTH in seven patients (87.5%) returned to normal during the 1-year follow-up. One patient had recurrent PHPT and PEIT was repeated.

Our study is limited by the small sample size and its retrospective, hospital-based nature. Since it is a single-center series, there may also be some selection bias. In addition, our assessment of the prevalence of PHPT in asymptomatic adults may be underestimated. Further large-scale, prospective research is needed to accurately determine the prevalence and clinical characteristics of PHPT in Taiwan.

Conclusion

This study confirms our suspicion that PHPT is underdiagnosed in Taiwan. Since it is a treatable disorder, it is important to be alert to this condition, particularly in the case of symptomatic individuals such as those with recurrent urolithiasis. Although still relatively uncommon, screening serum calcium levels helps diagnose PHPT at an asymptomatic stage.

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