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ORIGINAL ARTICLE

The characteristics of clinical changes in primary hyperparathyroidism in Chinese patients

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Abstract

In Western countries, the presentation of primary hyperparathyroidism (PHPT) changed from a symptomatic to an asymptomatic disease after the 1970s, whereas in China, only one study has evaluated the changing clinical characteristics and biochemical profiles of PHPT patients. The aim of this study was to explore changes in the clinical characteristics of PHPT in Chinese patients. Overall, 140 consecutive patients with PHPT were studied between January 1, 2010 and June 30, 2016. The patients were divided into two groups: 32 consecutive patients from January 1, 2010 to March 31, 2013 were included in group 1, and 108 consecutive patients from April 1, 2013 to June 30, 2016 were included in group 2. The most frequent complaints were ostealgia (46.02%), urolithiasis (41.59%), constipation (25.66%), fatigue (18.58%), polydipsia and polyuria (15.93%) and fracture history (15.04%). The number of cases in group 2 was 3.38-fold greater than that of group 1. The parathyroid hormone (PTH) and fasting blood glucose (FPG) levels were higher in group 1 than those in group 2 ($p=0.039$, $p<0.001$). In 62.14% of patients with PHPT, the proportion of the first diagnosis due to hypercalcemia found using a multichannel autoanalyzer in group 1 was lower than that found in group 2 ($p=0.039$), and the proportion of the first diagnosis due to parathyroid lesions captured using routine neck ultrasonography in group 1 was higher than in group 2 ($p=0.003$). The proportion of parathyroid carcinoma cases was higher in group 1 than group 2 ($p=0.036$). Cases of PHPT increased with time, but the proportion of parathyroid carcinoma cases was lower in group 1 than that in group 2. Over time, the first diagnosis switched from parathyroid lesions captured by routine neck ultrasound to hypercalcemia found by a multichannel autoanalyser. At our centre, PHPT in Chinese patients still demonstrates classic characteristics.

Keywords Primary hyperparathyroidism · Parathyroid carcinoma · Parathyroid hyperplasia · Parathyroid adenoma · Clinical characteristics

Introduction

Primary hyperparathyroidism (PHPT) is a disease characterized by hypercalcemia, which is attributable to autonomous overproduction of parathyroid hormone (PTH) [1]. PHPT is one of the most common endocrine disorders and has an estimated prevalence between 0.1 and 0.5% in the USA. Prior to the advent of the multichannel autoanalyser in the 1970s, classical PHPT most often presented as a symptomatic disorder with bone loss and kidney stones. However, with serum calcium values routinely available through biochemical screening tests, the clinical profile of the disease has evolved into a disorder that most commonly presents asymptomatically [2, 3]. Currently, in parts of the world where biochemical screenings are routine, up to 80% of PHPT patients have "asymptomatic" PHPT [4]. Although there is a worldwide trend for asymptomatic PHPT

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to become more dominant, symptomatic PHPT continues to be the predominant form of the disease observed in some countries, such as India, Iran, and Saudi Arabia [5–8]. In China, the prevalence of asymptomatic PHPT is lower than those in European and American countries [9]. To date, there have been few large epidemiological investigations of PHPT in China. Only one study by Yan et al. reported that the prevalence of the disease was 0.204% in middle-aged and elderly Chinese people living in Beijing [10]. However, the incidence of the disease has increased in recent years. Only five studies have reported more than 140 cases over the past 10 years in China [9, 11–14]. Of these, most studies have shown that the clinical and biochemical features of PHPT in Chinese patients are still classically symptomatic [11–14]. Only the study by Zhao et al. showed that the proportion of asymptomatic disease from 2007 to 2010 was 52.5%, and incidental parathyroid lesions (routine neck ultrasonography was performed for thyroid evaluation) were the leading cause of such changes [9]. In the current study, the changing clinical characteristics and biochemical profiles of PHPT patients (confirmed by surgery and pathology at our centre) were analysed.

Materials and methods

Patients

A total of 140 consecutive patients from the Beijing Shijitan Hospital, Beijing, China who were diagnosed by pathological and biochemical testing between January 1, 2010 and June 30, 2016 were retrospectively analysed. Diagnosis of PHPT was confirmed by the demonstration of persistent hypercalcemia (or high–normal serum calcium levels) in the presence of normal or elevated PTH concentrations. Patients with symptomatic findings showed a history of renal calculi, bone pain, pathologic fractures, bone shaft tumours, proximal muscle weakness (especially of the lower extremities), or nonspecific symptoms such as depression, lethargy, and vague aches and pains [1]. Asymptomatic PHPT was defined as serum calcium concentrations generally within 1 mg/dL of the upper limit of the normal range and a PTH level that was only modestly elevated, generally 1.5- to 2-fold above the upper limit of normal, and these patients lacked the obvious signs and symptoms of either excess calcium or PTH. [15] A definite diagnosis of parathyroid carcinoma (PC) was made when a parathyroid tumour had one of the following clinicopathological features: [16] (1) vascular invasion, (2) perineural invasion, (3) gross invasion into adjacent anatomical structures, and/or (4) metastasis. PC cases were evaluated by two of the same pathologists at the time of diagnosis in our hospital. The tumour diameter was defined as the size of the pathological lesions after operation surgery. If there were multiple lesions, the tumour diameter was defined as the size of the pathological largest lesions after operation surgery.

Ostealgia was defined as a generalized, progressive increase in bone and joint pain in weight-bearing sites such as the lower limbs and the lumbar spine [17]. Among the 140 patients, 109 were women and 31 were men. The female-to-male ratio was 3.52:1. The mean age of the female patients was 58.25 ± 13.46 years and that of the male patients was 59.48 ± 16.14 years. All diagnoses were determined by operation and pathology. A combination of multiple endocrine neoplasia type 2 (MEN-II) was identified in 1 case of PHPT. Patients with secondary or tertiary hyperparathyroidism were excluded from this study. Patients were divided into two groups: 32 consecutive patients from January 1, 2010 to March 31, 2013 were included in group 1, and 108 consecutive patients from April 1, 2013 to June 30, 2016 were included in group 2.

Methods

The patients underwent standard evaluations that included personal history, family history, physical examination, and blood and urinary biochemical tests. These tests included total serum calcium (SCa) (reference range 2.10–2.75 mmol/L), serum phosphate (SP) (0.97–1.62 mmol/L), aspartate aminotransferase (ALT) (7–40 U/L), alanine aminotransferase (AST) (13–35 U/L), blood urea nitrogen (BUN) (2.10–7.9 mmol/L), gamma-glutamyl transpeptidase (GGT) (7–45 U/L), creatine phosphate kinase (CK) (20–190 U/L), uric acid (UA) (149-416 μmol/L), blood creatinine (CRE) (35.0–80.0 μmol/L), total cholesterol (TC) (3.10–5.70 mmol/L), triglycerides (TG) (0.56–1.70 mmol/L), high-density lipoprotein cholesterol (HDL-C) (0.91–2.28 mmol/L), low-density lipoprotein cholesterol (LDL-C) (1.90–3.6 mmol/L), fasting plasma glucose (FPG) (3.9–6.1 mmol/L), alkaline phosphatase (ALP) (35–100 IU/L, ADVIA 2400, Siemens, Germany), and both 24-h urinary calcium (24 H-UCa) (2.05–7.5 mmol/24 h) and phosphate (24 H-UP) (14.0–41.98 mmol/24 h) excretion. The serum 25-hydroxyvitamin D [25(OH)D] concentration was measured with electrochemiluminescence (normal range 25(OH)D > 30 ng/mL; Roche, Germany). The intact serum immunoreactive PTH level was measured using an intact immunoradiometric assay (reference range, 15–65 pg/mL; Access Immunoassay Systems Uni-Cel DXI800, Beckman Coulter, USA). Bone mineral density (BMD) was determined using a dual-energy X-ray absorptiometer (DiS-Caovery Wi, Hologic, USA).

Statistics

All variables were examined for a normal distribution. Continuous variables are shown as the mean ± standard deviation (SD) or median (IQR), and between-group differences in these variables were compared using a Student's *t* test or the Mann–Whitney *U* statistic. Categorical variables are presented as a frequency or percentage. Intergroup comparisons were analysed using the χ^2 test or the Fisher's exact probability test. A two-sided *p* value ≤ 0.05 was considered statistically significant. All of the above analyses were performed using SPSS 22.0 software (SPSS, Inc, Chicago, IL, USA).

Results

The clinical manifestations of PHPT in symptomatic patients

The most frequent complaints were ostealgia (46.02%), urolithiasis (41.59%), constipation (25.66%), fatigue (18.58%), polydipsia and polyuria (15.93%) and fracture history (15.04%) (Table 1).

Comparison of the basic clinical features in groups 1 and 2

The proportion of patients younger than 50 years old was higher in group 1 than in group 2 ($p < 0.001$). Despite the finding that the proportion of patients younger than 50 years differed between the groups, there was no significant difference in the mean ages (54.9 ± 16.9 vs 58.5 ± 13.0 years, $p = 0.207$). Group 1 showed higher PTH and FPG levels than group 2 [median 290 (94.5–2603) vs 193 (40.6–2269) pg/mL, $p = 0.039$; mean 6.46 ± 2.41 vs 5.31 ± 0.85 mmol/L, $p < 0.001$]. There was no significant difference in diabetes frequency between groups 1 and 2, and there was a significant positive correlation between the PTH concentration and FPG ($r = 0.290$, $p = 0.001$). There were no significant differences in height, weight, body mass index (BMI), ALT, AST, ALP, GGT, TC, TG, HDL-C, LDL-C, BUN, CRE, SCa, SP, 24 H-UCa and 24 H-UP between groups 1 and 2. There were no significant differences in the diameter of the lesion, serum 25(OH)D, BMD, *T* score and *Z* score between groups 1 and 2. There was also no significant difference in sex frequency between groups 1 and 2. The number of cases in group 2 was 3.38-fold greater than that of group 1 (Table 2).

Table 1 Clinical manifestations of PHPT in symptomatic patients ($n = 113$)

Symptoms	No. (%)
Ostealgia	52 (46.02%)
Urolithiasis	47 (41.59%)
Constipation	29 (25.66%)
Fatigue	21 (18.58%)
Polydipsia and polyuria	18 (15.93%)
Fracture history	17 (15.04%)
Nausea and vomiting	6 (5.31%)
Psychiatric symptoms	3 (2.65%)
Gastric ulcer	2 (1.77%)
Depression	1 (0.88%)

Comparison of the proportion of different pathologies between groups 1 and 2

There were six (18.75%) patients with PC in group 1 and 7 (6.48%) patients with PC in group 2 ($p = 0.036$). The proportions of parathyroid hyperplasia (PH) and parathyroid adenoma (PA) did not differ between the two groups (Fig. 1).

A comparison of the primary reason for the first diagnosis between group 1 and group 2

Among patients with ostealgia, a first diagnosis due to this symptom was observed in 7 (21.88%) patients in group 1 and 26 (24.07%) patients in group 2; this was the most frequent symptom, but there was no significant difference between the groups ($p = 0.797$). Among 62.14% of patients with PHPT, a first diagnosis due to hypercalcemia, as determined by multichannel autoanalyser, was found in 8 (25.00%) patients in group 1 and 49 (45.37%) patients in group 2 ($p = 0.039$). Among 62.14% of patients with PHPT, a first diagnosis due to parathyroid lesions, as determined using routine neck ultrasonography for thyroid evaluation, was found in 13 (40.63%) patients in group 1 and 17 (15.74%) patients in group 2 ($p = 0.003$). In our study, 19.29% of patients with PHPT were asymptomatic (Table 3).

Discussion

The aetiology of PHPT includes PC (< 1–5%), parathyroid hyperplasia (10–15%), and parathyroid adenoma (80–85%) [18–21]. There were 140 PHPT patients in our centre, including 13 (9.29%) cases of PC, 27 (19.29%) cases of parathyroid hyperplasia, and 100 (71.43%) cases of parathyroid adenoma. There was a 3.38-fold increase in the number of PHPT patients admitted to our department from January 1, 2010–March 31, 2013 to April 1, 2013–June 30, 2016. There was an increase in diagnoses due to the wide application of routine biochemical analysis and thyroid ultrasonography for thyroid evaluation. The proportion of PC cases in our centre was higher than those previously reported in other countries,

Table 2 A comparison of basic clinical features between group 1 and group 2

	Group 1 ($n=32$)	Group 2 ($n=108$)	p
Age (years)	54.9 ± 16.9	58.5 ± 13.0	0.207
< 50 years	12/32 (37.5%)	23/108 (21.3%)	< 0.001
Diabetes	6/32 (17.85%)	17/108 (15.74%)	0.687
Duration (months)	24 (1–132)	18 (1–260)	0.393
Sex (female/men)	23/9	86/22	0.353
Height (cm)	159.5 ± 8.0	162.0 ± 7.6	0.332
Weight (kg)	62.6 ± 9.6	61.4 ± 12.4	0.634
BMI (kg/m^2)	24.6 ± 4.7	23.3 ± 4.1	0.334
Diameter (cm)	2.00 ± 1.31	2.05 ± 1.50	0.866
SCa (mmol/L)	3.96 ± 0.54	2.82 ± 0.34	0.092
SP (mmol/L)	0.82 ± 0.26	0.86 ± 0.29	0.556
PTH (pg/mL)	290 (94.5–2603)	193 (40.6–2269)	0.039
Serum25(OH)D (ng/mL)	9.1 (4.5–31)	10.6 (5.4–33.2)	0.107
24 H-UCa (mmol/L)	8.23 ± 3.56	8.79 ± 3.58	0.595
24 H-UP (mmol/L)	12.43 ± 8.48	15.30 ± 7.33	0.206
ALP (IU/L)	255 ± 493	158 ± 223	0.291
ALT (IU/L)	17.44 ± 6.54	19.41 ± 11.05	0.340
AST (IU/L)	24.47 ± 11.07	21.63 ± 14.93	0.322
GGT (IU/L)	21.34 ± 17.04	23.93 ± 16.08	0.435
CK (IU/L)	56.60 ± 28.58	65.69 ± 60.32	0.426
BUN (mmol/L)	5.19 ± 1.84	5.39 ± 1.97	0.618
CRE (μmol/L)	79.00 ± 43.83	64.85 ± 31.97	0.448
UA (mmol/L)	337.81 ± 122.25	340.56 ± 105.14	0.901
FPG (mmol/L)	6.46 ± 2.41	5.31 ± 0.85	< 0.001
TC (mmol/L)	4.70 ± 1.19	4.59 ± 0.83	0.591
TG (mmol/L)	1.64 ± 0.91	1.47 ± 0.84	0.331
HDL-C (mmol/L)	1.28 ± 0.54	1.23 ± 0.34	0.499
LDL-C (mmol/L)	2.73 ± 0.97	2.41 ± 0.81	0.066
BMD_{L2-4} (g/cm^2)	0.740 ± 0.014	0.740 ± 0.013	0.672
T_{L2-4}	− 2.71 ± 1.43	− 2.55 ± 1.52	0.589
Z_{L2-4}	− 1.80 ± 1.45	− 1.58 ± 1.58	0.482
$BMD_{Femoral\ neck}$ (g/cm^2)	0.699 ± 0.014	0.700 ± 0.014	0.912
T_{Neck}	− 1.51 ± 1.22	− 1.20 ± 1.11	0.186
Z_{Neck}	− 1.61 ± 1.26	− 1.62 ± 1.12	0.223
$BMD_{Total\ hip}$(g/cm^2)	0.690 ± 0.182	0.74 ± 0.186	0.153
$T_{Total\ hip}$	− 2.02 ± 1.39	− 2.03 ± 1.40	0.991
$Z_{Total\ hip}$	− 1.40 ± 1.41	− 1.39 ± 1.44	0.988

BMI body mass index, *SCa* serum calcium, *SP* serum phosphate, *PTH* parathyroid hormone, *24 H-UCa* 24-h urinary calcium, *ALP* alkaline phosphatase, *ALT* aspartate aminotransferase, *AST* alanine aminotransferase, *GGT* gamma-glutamyl transpeptidase, *CK* creatine phosphate kinase, *BUN* blood urea nitrogen, *CRE* blood creatinine, *UA* uric acid, *FPG* fasting plasma glucose, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *BMD* bone mineral density

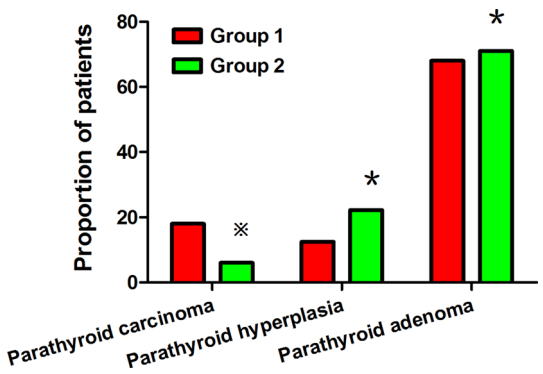

Fig. 1 Comparison of the proportions of different pathologies. There is a difference in parathyroid carcinoma (p value = 0.036). There is no between-groups difference in parathyroid hyperplasia and adenoma (*p value > 0.05)

Table 3 A comparison of the primary reason for the first diagnosis between group 1 and group 2

	Group 1 ($n=32$)	Group 2 ($n=108$)	p
With symptoms			
Ostealgia	7 (21.88%)	26 (24.07%)	0.797
Fracture	2 (6.25%)	3 (2.78%)	0.321
Renal calculus	2 (6.25%)	14 (12.96%)	0.364
Total	11 (34.38%)	42 (38.89%)	0.644
With no symptoms			
Hypercalcemia found	8 (25.00%)	49 (45.37%)	0.039
Parathyroid lesions found	13 (40.63%)	17 (15.74%)	0.003
Total	21 (65.62%)	66 (61.11%)	0.644

but this proportion decreased from 18.75% in group 1 to 6.48% in group 2, which is in agreement with other studies from China [9, 11–13]. Patients with PHPT in our hospital came from seventeen provinces in China, and the percentage of PC reached up to 9.29%. A possible reason for such a high percentage was that our hospital, Beijing Shijitan Hospital, is a tertiary care centre that specializes in endocrine surgery in patients with severe disease. This suggests that patients with a greater probability of PC tend to come to our hospital. There were only two cases that underwent surgery for the first time in our hospital, while 11 recurrent cases underwent surgery at other hospitals.

PHPT is observed primarily in postmenopausal women (female-to-male ratio of 3–4:1) over 50 years of age [22, 23] In the current study, the female-to-male ratio was similar to that of other studies [22–25] The proportion of patients younger than 50 years in group 2 was lower than that in group 1, and the PTH and FPG levels were significantly lower as well. The reasons for these changes may be associated with the decreased proportion of PC and the wide

application of routine biochemical analysis and thyroid ultrasonography for thyroid evaluation, resulting in the diagnosis being made earlier.

Reportedly, the prevalence of diabetes mellitus in PHPT patients is approximately 8%, and the prevalence of PHPT in diabetic patients is approximately 1%. Insulin resistance is present in hyperparathyroidism, and it may arise from an increased intracellular free calcium concentration, which decreases the normal insulin-stimulated glucose transport and increases the requirement for insulin. If this insulin resistance progresses, impaired glucose tolerance and diabetes mellitus can occur [26–28]. In this study, we observed PHPT with diabetes in 6/32 cases (25.0%) in group 1 and in 17/108 cases (15.74%) in group 2, which was higher than the rate reported by Taylor et al. [26]. This difference may be because the clinical manifestations of patients in our study were of the classical type and the disease seemed to be more severe. Our study also demonstrated a significant positive correlation between PTH concentrations and FPG, which is not in agreement with the study by Zhao et al. showing a significant positive correlation between PTH concentrations but not with fasting plasma glucose [9].

Vitamin D deficiency is common among PHPT patients compared to the general population in Western countries [29, 30]. A study by Man RE et al. showed that approximately 75% of adults had suboptimal 25(OH)D concentrations in a population-based sample of Asian adults in China [31]. There have been three reports regarding the vitamin D levels of Chinese PHPT patients [9, 14, 32]. In our study, there was no change in vitamin D levels. We found that the vitamin D levels were similar to those described by Silverberg from Beijing and those of studies reporting the vitamin D levels of symptomatic PHPT patients in Shanghai, China [9, 14].

In Western countries, the presentation of PHPT changed from a symptomatic to an asymptomatic disease after the 1970s [15, 33, 34], whereas in China, patients are largely still symptomatic and exhibit classic disease manifestations. Symptomatic patients have been reported for the last 10 years in China [11–14, 35, 36], with skeletal system manifestations (33.1–62.2%) and urinary system manifestations (8.9–55.14%) as the main complaints. In this study, the most frequent symptom for the first diagnosis in the two groups was ostealgia. Among 62.14% of patients with PHPT, the first diagnosis most frequently occurred because hypercalcemia was found using a multichannel autoanalyser. The reason for the increase in diagnosis of PHPT by hypercalcemia may be the wide application of multichannel autoanalyzers. The reason for the decrease in diagnosis by ultrasound may be operator-dependent or because of the improvement of the multichannel autoanalyser. This finding is not in agreement with that of the study by Zhao et al., which showed incidental parathyroid lesions captured by routine neck ultrasonography for thyroid evaluation.

Most patients from the USA and Europe whose PHPT is discovered in this manner do not show overt skeletal or renal complications. However, other Asian countries such as India, Iran, Saudi Arabia and Thailand have reported a widespread prevalence of symptomatic disease with skeletal manifestations [34]. For many years, it was believed that the negative effects of PHPT on the skeleton were restricted to cortical bone [37]. There was only one report on BMD in Chinese PHPT patients [9]. In our study, the $BMD_{Femoral\ neck}$ and $BMD_{Total\ hip}$ were similar to those in the study by Zhao et al. for patients with symptomatic PHPT [9]. We also observed no change in $BMD_{Femoral\ neck}$ and $BMD_{Total\ hip}$ over the past 6 years, and the clinical manifestations of patients remained classical in our centre.

Some potential limitations of this study should be addressed. First, the included patients with PHPT from seventeen provinces in China were more likely to have overt disease and show a classic presentation. Because this was a single-centre, hospital-based study, further prospective studies with a large number of patients from a community-based population would provide a better picture of the disease in China. Second, selection bias was present in this retrospective and hospital-based study. However, the PHPT patients were confirmed through pathological and biochemical testing, and such potential selection biases were minimized. Third, the number of patients in group 1 was small. Finally, the BMD, *T* score, *Z* score and vitamin D data were not available for all patients.

In conclusion, the results derived from our centre revealed some changes in PHPT in recent years. For instance, there was a 3.38-fold increase in the number of PHPT patients, and the proportion of PC cases decreased. The first diagnosis in patients presenting with PHPT symptoms was mainly due to ostealgia symptoms, and this did not change over time. Approximately, 62.14% of patients with PHPT were recognized by examination for the first time. A first diagnosis in those patients changed from parathyroid lesions captured by routine neck ultrasonography to hypercalcemia found by a multichannel autoanalyser. These data demonstrate that the overall clinical and biological features of PHPT from 2010 to 2016 in our centre remained classic despite improvements in the availability of the multichannel autoanalyser.

Acknowledgements This study was approved by the Ethical Committee of Beijing Shijitan Hospital, Capital Medical University and was performed in accordance with the approved guidelines and regulations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests.

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