Clinical Presentation of Primary Hyperparathyroidism in Older Adults

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Background: The clinical presentation of primary hyperparathyroidism (PHPT) has changed greatly during the past few decades. Our aim was to evaluate whether the clinical presentation at diagnosis differed according to age.

Methods: We evaluated retrospectively a monocentric series of 462 consecutive patients with PHPT, dividing them according to a cutoff of 65 years of age.

Results: No differences were found in the mean serum PTH, calcium, or vitamin D levels. In older patients (n = 212; 45.9%), the urinary calcium levels were significantly lower (median, 205 mg/24 hour; interquartile range, 220 mg/24 hour) compared with those in younger patients (median, 308 mg/24 hour; interquartile range, 233 mg/24 hour). In addition, renal involvement was significantly less frequent (25% vs 49.2%), and bone involvement significantly more frequent (58% vs 44%) in older patients compared with younger patients. The clinical presentation was significantly different between the two age groups, with a lower frequency of symptomatic forms and a greater frequency of asymptomatic forms not meeting surgical criteria in the older patients (44.4% vs 57.2% and 18.4% vs 5.6%, respectively). Osteoporosis was significantly more frequent in the older adults than in their younger counterparts. The most affected bone site was the forearm in older adults and the lumbar spine in younger ones (50.3% and 50.5%, respectively).

Conclusion: The clinical presentation of PHPT differs according to age, and this difference can affect the selection of management modalities.

Freeform/Key Words: primary hyperparathyroidism, clinical presentation, disease management

The clinical and epidemiological presentation of sporadic primary hyperparathyroidism (PHPT) has changed profoundly during the past few decades, shifting to a largely asymptomatic disease [1]. Genetic and demographic factors have been recognized to influence the PHPT presentation [2, 3]. However, it is also conceivable that technological advances in laboratory assessments and the introduction of osteoporosis screening have played important roles in western countries [3, 4]. This transition has also been registered more recently in some developing countries, such as China [5] and Brazil [6].

Few data are available regarding the influence of aging on the clinical presentation of PHPT, in particular its effect on disease management for patients >65 years (*i.e.,* older adults) [7, 8]. We, thus, evaluated a large unselected series of sporadic PHPT, assessing the

Abbreviations: 25OHD, 25-hydroxy-vitamin D; BMD, bone mineral density; PHPT, primary hyperparathyroidism.

Received 19 August 2019
Accepted 26 September 2019
First Published Online 2 October 2019

ISSN 2472-1972
December 2019 | Vol. 3, Iss. 12
doi: 10.1210/js.2019-00316 | Journal of the Endocrine Society | 2305–2312

clinical features and the likelihood of meeting the surgical criteria recommended by current guidelines for older adults compared with younger adults.

1. Patients and Methods

A. Design

A retrospective survey was conducted of the medical records of all patients with a diagnosis of PHPT who had attended our department from January 1997 to June 2018. The institutional review board and the ethical committee of our institution approved the present study, which was conducted in accordance with the Declaration of Helsinki. No informed consent was required from the patients for the present study because we only retrospectively accessed a de-identified database for analysis purposes. All data had been collected as part of the routine clinical and psychological procedures.

B. Patients

The patients had been referred by general practitioners, primary care clinics, and subspecialty clinics. The PHPT diagnosis had been established by the presence of hypercalcemia and concomitant inappropriately elevated serum PTH levels on at least two separate occasions (reference range: calcium, 8.4 to 10.2 mg/dL; PTH, <65 ng/L; for details see *Methods*). Pregnant patients were also excluded. Patients with a diagnosis of multiple endocrine neoplasm, hyperparathyroidism-jaw tumor syndrome, familial hypocalciuric hypercalcemia, or parathyroid carcinoma were excluded. None of the included patients had been taking calcium or vitamin D supplements, estrogen or testosterone or selective estrogen receptor modulators, or bone-active medications for at least 6 months.

In line with the study by Bilezikian *et al.* [9], patients were classified as having asymptomatic PHPT if they lacked radiological signs of bone involvement, nephrolithiasis, and symptoms of hypercalcemia. Regarding bone involvement, all patients had routinely undergone dual X-ray absorptiometry and a radiographic evaluation of the skull and hands to check for signs of excess PTH effects on bone, such as osteitis fibrosa, subperiosteal resorption in the fingers, salt and pepper mottling of the skull, and/or brown tumors. Regarding kidney involvement, the patients were classified as symptomatic if they had a recorded positive history for renal stones (ultrasound examination, urography, plain radiography, a history of passing stones, or endoscopic or surgical removal) or if renal stones (or calcinosis) had been diagnosed by routinely performed ultrasonography in asymptomatic or symptomatic patients at physical examinations.

The criteria for surgery reported in the latest guidelines were retrospectively applied to all included patients. Patients with asymptomatic PHPT not meeting the surgical criteria provided by the updated international guidelines were considered “mild asymptomatic” patients [10]. Patients with PHPT who were aged >65 years were considered “older adults.” This cutoff has been recently used to identify people with the concurrent comorbidity burden that accompanies senescence [11–13].

C. Methods

All blood samples were collected after overnight fasting and rest. The serum total calcium and creatinine levels were assayed using automated analysis and colorimetric and enzymatic methods, and ionized serum calcium was analyzed using a specific probe after pH correction.

The estimated glomerular filtration rate was calculated using the CKD-EPI (chronic kidney disease-epidemiology collaboration) equation [14]: estimated glomerular filtration rate = $141 \times \min(\mathrm{SCr}/k,1)\alpha \times \max(\mathrm{SCr}/k,1) - 1.209 \times 0.993 \times \mathrm{age}$ ($\times$ 1.018 if women) ($\times$ 1.159 if black), where SCr represents serum creatinine (in mg/dL), k is 0.7 for women and 0.9

for men, α is −0.329 for women and −0.411 for men, min represents the minimum of SCr/k or 1, and max represents the maximum of SCr/k or 1.

Serum intact PTH concentrations were measured up to 2012 using a two-site immunochemiluminometric assay (Immulite 2000; DPC, Los Angeles, CA) with inter-and intra-assay variation coefficients of 6.3% to 8.8% and 4.2% to 5.7%, respectively [15]. Thereafter, serum intact PTH concentrations were measured using a new second-generation immunochemiluminometric assay (Cobas e411; Roche Diagnostics, Milan, Italy) [16], with inter- and intra-assay variation coefficients of 3.1% to 6.5% and 1.4% to 3.2%, respectively. The corresponding normal ranges are 20 to 65 ng/L and 15 to 65 ng/L.

The serum 25-hydroxy-vitamin D (25OHD) levels were measured using a radioimmunoassay (DIAsource 25OHVit. D3-Ria-CT Kit; DIAsource Immuno Assays S.A., Nivelles, Belgium) [17], with a detection limit of 0.6 μg/L (1.5 nmol/L) and inter- and intra-assay variation coefficients of 5.3% and 4.7%, respectively. Our laboratory periodically conducts quality control tests on kits used with material provided by the manufacturer and is a member of the External Quality Assessment Scheme for the estimation of 25OHD, conducted by QualiMedLab-CNR (Pisa, Italy), as a method of determining the accuracy of the results. A level <20 μg/L was considered the cutoff for deficiency.

The bone mineral density (BMD) was measured at the lumbar spine (L2 to L4), proximal femur, and distal third of the nondominant radius using the same instrument (dual X-ray absorptiometry; QDR-4500; Hologic, Bedford, MA) throughout the study period. Minor upgrades to the BMD instrument, in particular, in the reporting and duration of the procedure, did not significantly affect the results. Data were analyzed as absolute measurements (in grams per square centimeter) and reported as T- and Z-scores.

All patients underwent standard renal ultrasound examinations using a 2- to 5-MHz-wide band convex transducer. For a definitive diagnosis of stones, which enables patients' condition to be classified as positive or negative for nephrolithiasis, radiologists looked for hyperechogenic spots that were >2 mm in diameter with a multiplanar evaluation of specific signs such as echogenicity, posterior acoustic shadowing, or a positive twinkle sign. Preoperative localization was considered positive when at least one of the performed imaging studies (neck ultrasound scan and/or technetium-99m-sesta-methoxyisobutylisonitrile parathyroid scintigraphy) had clearly identified the adenoma.

D. Statistical Analysis

The variables were preliminarily tested for normal distribution using the Shapiro-Wilks W test, and data are presented as the mean ± SD when normally distributed and median and interquartile range when not normally distributed. Continuous variables with non-normal and normal distribution were analyzed using the Mann-Whitney U test and t test for unpaired samples, respectively, as appropriate. Differences in categorical variables were analyzed using the χ^2 test. The level of statistical significance was set at $P \leq 0.05$. Calculations were performed using IBM SPSS Statistics, version 21 (IBM Corp., Armonk, NY).

2. Results

The data from 462 consecutive patients with a diagnosis of sporadic PHPT during the study period were analyzed. Of the 462 patients, 212 (45.9%) were aged >65 years. The demographic, clinical, and biochemical features of the whole series are summarized in Table 1, with a comparison between patients aged <65 and >65 years. No differences were found in the sex distribution or mean serum PTH, calcium, and 25OHD levels. The urinary calcium levels were higher in younger patients, renal involvement was significantly more frequent in younger patients, and bone involvement was significantly more frequent in older patients. The most affected bone site was the lumbar spine in the younger patients and the forearm in the older patients.

Table 1. Demographic and Clinical Characteristics

Characteristic	Whole Series (n = 462)	Patients Aged <65 y (n = 250)	Patients Aged ≥65 y (n = 212)	*P* Value[a]
Age, y	61.3 ± 13.1	51.9 ± 10.1	72.3 ± 5.5	<0.0001[b]
Sex				0.408
Male	108 (23.4)	60 (24)	48 (22.6)	
Female	354 (76.6)	190 (76)	164 (77.4)	
PHPT status				<0.0001[b]
Symptomatic	237 (51.3)	143 (57.2)	94 (44.4)	
Asymptomatic, meeting surgical criteria	172 (37.2)	93 (37.2)	79 (37.3)	
Mild asymptomatic	53 (11.5)	14 (5.6)	39 (18.4)	
PTH (ng/L)	127.5 [130]	124 [124]	139 [133]	0.36
Total serum calcium (mg/dL)	11.2 ± 1.1	11.2 ± 1.2	11.2 ± 1.1	1
Ionized serum calcium (mmol/L)	1.45 ± 0.2	1.45 ± 0.2	1.46 ± 0.2	0.592
Urinary calcium (mg/24h)	255 [250]	308 [233]	205 [220]	<0.0001[b]
25OHD (μg/L)	24 [20]	25 [18]	22.5 [22]	0.535
eGFR (mL/min/1.73 m^2)	71 ± 16.6	82.3 ± 11.4	61.6 ± 14.2	0.003[b]
Presence of kidney stones	176 (38.1)	123 (49.2)	53 (25)	<0.0001[b]
Presence of osteitis fibrosa cystica	100 (21.6)	41 (16.4)	59 (27.8)	0.003[b]
Lumbar T-score	−2.4 ± 1.5	−2.3 ± 1.4	−2.6 ± 1.5	0.124[b]
Femoral T-score	−2 ± 1.2	−1.8 ± 1.2	−2.3 ± 1.1	<0.0001[b]
Distal third radius T-score	−2.4 ± 1.6	−1.9 ± 1.5	−3.1 ± 1.5	<0.0001[b]
Lumbar Z-score	−1 ±1.5	−1.3 ± 1.4	−0.6 ± 1.5	<0.0001[b]
Femoral Z-score	−0.7 ± 1.2	−0.8 ± 1.2	−0.5 ± 1.1	0.0103[b]
Distal third radius Z-score	−1.1 ± 1.4	−1 ± 1.4	−1.1 ± 1.4	0.446[b]
Osteoporosis at any site	233 (50.4)	110 (44)	123 (58)	0.0036[b]
Location of worst T-score, %				<0.0001[b]
At lumbar site	39.5	50.5	26.9	
At femoral site	20.1	17.7	22.8	
At distal radius site	40.4	31.8	50.3	
Hypertension	177 (38.3)	61 (24.4)	116 (54.7)	<0.0001[b]
Diabetes mellitus	32 (7)	9 (3.6)	23 (10.8)	0.0041[b]
Positive imaging findings for PHPT localization	336/454 (74)	190/248 (76.6)	146/206 (70.8)	0.1582

Data presented as mean ± SD for normally distributed variables, median [IQR] for non-normally distributed variables, and absolute numbers and percentages for categorical variables.

Abbreviation: eGFR, estimated glomerular filtration rate; IQR, interquartile range.

[a]The comparison was performed between patients aged <65 and >65 y.

[b]Statistically significant.

Among the asymptomatic patients, other than age, osteoporosis was the most common criterion for surgery met in both age groups (43% of younger and 50% of older patients). The prevalence of "mild asymptomatic" patients was significantly greater in the older group.

The rate of preoperative localization (not performed in eight patients) stratified by the clinical presentation is presented in Table 2. No differences were found among the clinical subgroups of younger patients, although positive imaging findings were significantly less frequent in the "mild asymptomatic" older patients.

3. Discussion

The present study has shown that the clinical presentation of PHPT is greatly influenced by aging. In older adults, the disease was more frequently asymptomatic and mostly characterized by bone involvement. In contrast, younger patients were more often symptomatic and mainly affected by renal impairment. This finding did not seem to be related to biochemical disease activity, which was similar in the two age groups. In addition, among the asymptomatic patients, the likelihood of meeting the surgical criteria suggested by the latest guidelines was significantly lower in the older adults.

The clinical profile of PHPT in western countries has changed profoundly during the past few decades, from a highly symptomatic disease, characterized by symptoms of hypercalcemia and kidney and bone involvement, to a largely asymptomatic disease [1–4]. Several factors were involved in this transition. In particular, the technological advances in laboratory assessments and the introduction of osteoporosis screening have played important roles. In addition, the ethnic, geographic [4], and demographic [18] characteristics of the population have been the main factors influencing the epidemiological and phenotypic presentation of PHPT [3, 4].

Although age <50 years is one of the criteria for surgery indicated by the guidelines for asymptomatic PHPT [9, 19], owing to the natural history of disease in this age group [19], to date only a few studies have evaluated the effect of age on the clinical presentation of PHPT [7, 8, 20, 21]. Some studies of the clinical features of juvenile PHPT have been recently reported [20, 21]. These patients were reportedly equally [21] or more [20] symptomatic than their adult counterparts.

However, data on PHPT in older adults are limited [8]. In the 1990s, in a surgical series, Udén *et al.* [8] showed that renal stones were significantly more common in younger patients (aged <60 years), despite the findings of no differences in the biochemical profile of PHPT between the two groups (in agreement with our findings). However, in the study by Udén *et al.* [8], the PHPT symptoms and signs were evaluated only using a patient self-report questionnaire, and radiological and/or densitometric data of bone involvement were not available.

To the best of our knowledge, our study is the first to have evaluated the clinical profile of PHPT in older adults in an unselected series. The clinical profile of PHPT differed greatly between our younger and older patients. Older patients were less frequently symptomatic and had a predominance of bone involvement. It is clear that the frequent evaluation of serum calcium levels using automated multichannel analyzers and osteoporosis screening in

Table 2. Positive Imaging Findings for Preoperative Localization of PHPT Stratified by Clinical Presentation and Age at Diagnosis

Patient Age, y	Symptomatic PHPT	Asymptomatic PHPT Meeting Surgical Criteria	Mild Asymptomatic PHPT	*P* Value
<65 (n = 248)	110 (77.5)	70 (76.1)	10 (71.4)	0.869
≥65 (n = 206)	70 (76.1)	56 (72.7)	20 (62.5)	0.041[a]

Data presented as absolute numbers and percentages.
[a]Statistically significant.

postmenopausal women might account for the greater proportion of asymptomatic PHPT cases in the older group [5, 21].

In our series, renal stones had developed significantly less frequently in the older patients, which is also the case in the general population [22]. Data from epidemiological studies have highlighted the correlation of urine calcium excretion with the risk of stone formation in the general population [23] and in patients with PHPT [24, 25]. Also, in our series, calcium excretion was significantly greater in younger patients.

In contrast, the presentation of PHPT in older adults was characterized by a predominance of bone involvement. As expected, osteoporosis was significantly more frequent in the older adults than in their younger counterparts. However, the bone sites were involved differently, with the cortical bone more affected in the older adults and the cancellous bone more affected in the younger patients. In addition, radiological signs of osteitis fibrosa were more frequently reported in the older group. The lack of differences in the serum 25OHD, calcium, or PTH levels between the two groups appears to rule out the role of disease activity in the bone manifestations.

An observational study of the natural history of asymptomatic PHPT showed that BMD was maintained at the lumbar spine for 15 years but was progressively lost at the cortical level [26]. The investigators hypothesized that the low turnover rate of the cortical bone and time-dependent cortical bone resorption induced by PTH excess might have played a role [26].

Our data have extended our previous findings on the sex differences in PHPT, which were related to the menopausal state [18]. With the data from our study, a combined sex-and age-dependent different target organ sensitivity to PTH excess could be hypothesized, as reported in an experimental hyperparathyroidism model [27].

The different clinical profile of PHPT will have an effect on disease management because older adults will be less often symptomatic and more frequently "mildly asymptomatic." Accordingly, clinical surveillance would be an appropriate option for a greater proportion of older adults than for younger ones, and surgery is indicated for almost all patients. This issue is of considerable importance because older adults frequently have a large burden of comorbidities [28], and this age group represents a considerable portion of the patients with PHPT [1].

The propensity of older adults to undergo a surgical procedure for an asymptomatic disease is reduced. The lower preoperative localization rate in older adults with "mild asymptomatic" PHPT limited the possibility of a minimally invasive approach, which has been associated with a lower incidence of pain and complications and a shorter hospital stay [29].

Our study had some limitations. Despite the large cohort, we performed a retrospective single-institution study, which could have been affected by a selection bias. Our findings, therefore, should not be generalized indiscriminately to patients with PHPT in other countries and ethnic groups. However, unlike previous studies, we evaluated a large and unselected series of consecutive patients with PHPT, who had undergone full biochemical and clinical investigations. Our study results, thus, better reflect real-life clinical practice. A second limitation was the lack of information on the disease duration before the diagnosis. Moreover, although we excluded patients taking bone-active medications in the previous 6 months, we could not rule out a bone effect of these drugs when taken more remotely. Finally, we acknowledge that we did not use the reference standard liquid chromatography aligned to mass spectrometry to assess the 25OHD levels and also that our RIA might have slightly overestimated the 25OHD levels (in line with several RIAs). However, all measurements were performed in the same laboratory, thereby ensuring good quality of the data.

In conclusion, the clinical presentation of PHPT is greatly influenced by aging. In older adults, the disease was more frequently asymptomatic and characterized by a predominance of bone involvement. According to recent guidelines, the conservative approach will be an appropriate option in a non-negligible proportion of older patients with PHPT. In contrast, the great majority of patients aged <65 years will meet the criteria for surgery, highlighting the default surgical indication for virtually all patients in the younger age group.

Additional Information

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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