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Research Article

Comparison between Sporadic Primary Hyperparathyroidism and Multiple Endocrine Neoplasia Associated Primary Hyperparathyroidism: Retrospective Analysis of Indian PHPT Registry

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Abstract

Introduction: Despite heterogeneity, the most consistent presentation of multiple endocrine neoplasia (MEN) is primary hyperparathyroidism (PHPT) seen in almost 100% of cases in MEN-1 and nearly 30% in MEN-2A. This retrospective study was planned to compare the demography, clinical manifestations, management, and outcome of sporadic PHPT (s-PHPT) and multiple endocrine neoplasia (m-PHPT) patients.

Methodology: This was a registry-based (www.indianphptregistry.com) retrospective cohort study from a tertiary care hospital in North India. In this study, medical records, and clinical data of s-PHPT patients and genetically proven and clinically suspected m-PHPT patients were analyzed.

Result: A total of 616 PHPT patients have been registered in the electronic registry, and 72 (11.68%) patients had m-PHPT. The mean age of s-PHPT and m-PHPT patients was 43.4 ± 14.3 and 35.8 ± 13.5 years ($p < 0.05$) respectively. The multiglandular disease was common in m-PHPT (40.2%) compared to s-PHPT (6%). Both s-PHPT and m-PHPT had comparable mean calcium, mean phosphate, and median PTH but the median 25(OH) vitamin D (25OHD) level was more in s-PHPT as compared to m-PHPT. Median post-surgery falls in parathyroid hormone (PTH), and calcium were more in the patients of s-PHPT compared to m-PHPT 84.8% vs 46.7% and 23.4% vs 16.6% respectively ($p < 0.05$).

Conclusion: This study showed that m-PHPT patients presented at a young age had more asymptomatic presentation and multiglandular disease without significant differences in serum biochemistry. Percent fall in PTH and calcium were more in s-PHPT patients in the post-surgery period with less incidence of recurrent and persistent disease.

Keywords: Primary Hyperparathyroidism; Multiple Endocrine Neoplasia; MEN-1; Hypercalcemia

Introduction

Primary hyperparathyroidism (PHPT) is a common disease with a prevalence of nearly 3 cases per 1000 in the general population. Prevalence is more in females and in aged patients (> 65 years) [1,2].

Etiologically PHPT is mostly sporadic [3], however, a significant proportion of patients develop PHPT as part of familial syndrome viz. multiple endocrinal neoplasia (MEN) type 1 or 2A syndrome, hyperparathyroidism jaw tumor syndrome and familial isolated parathyroid adenoma syndrome [4-6]. As many as 18% of PHPT patients might have other MEN-associated tumors at presentation [6-8].

Spectrum of MEN-1 associated tumors includes parathyroid and pituitary adenoma, and pancreatic-duodenal neuroendocrine tumors, whereas pheochromocytoma, medullary thyroid carcinoma along with PHPT are seen in MEN-2A [9,20]. Among mutation-positive MEN cases, family history was not observed in nearly 30% of cases. Lack of family history and another tumoral expression might confuse clinicians and led to an underestimation of the current scenario [10,11]. Considering the current guideline, testing for MEN genetics is considered only in cases of positive family history and the presence of a tumor spectrum consistent with MEN [12].

Though surgery is the mainstay of management for all forms of PHPT, the extent of surgery and follow-up strategy might differ if the familial disease could be suspected in each case.

There are very few studies available to address the difference in presentation, management, and outcome of s-PHP and m-PHPT in literature, and there is a scarcity of data from the Indian subcontinent also. Thus, the present study was planned to provide a broad insight into this topic after comparing the demography, clinical manifestations, management, and outcome of s-PHPT and m-PHPT patients presented in a tertiary care hospital in North India. This article was previously presented as a meeting abstract at the Endocrine society conference, US ENDO 2023.

Methodology

This study was a registry-based (www.indianphptregistry.com) retrospective cohort study from a tertiary care hospital in North India. This study was approved by institute ethics committee of PGIMER, Chandigarh vide reference number: NK/499/Res/1150. The medical records and clinical data of s-PHPT patients and genetically proven and clinically suspected m-PHPT patients registered in the Indian PHPT registry between 2012 to 2022 were analyzed in terms of their demography, clinical presentation, and biochemical and hormonal parameters at the time of presentation. Therapeutic strategies were also analyzed along with outcomes in terms of the percent fall of calcium and PTH as compared to the baseline.

Before incorporating patients' data into the Indian PHPT registry, the presence of MEN syndrome was confirmed by taking a detailed personal and family history, conducting a thorough clinical examination including cutaneous examination, abdominal ultrasonography, and measuring serum level biochemical

parameters and hormonal assessment, viz. parathyroid hormone, pituitary hormone profile, gastrin, calcitonin, insulin, and c-peptide. Tumor markers such as procalcitonin and carcinoembryonic antigen (CEA), metanephrine, normetanephrine, and 3-methoxy tyramine were also analyzed on cases to case basis. Any biochemical abnormality was further corroborated with imaging.

Genetical analysis was done after taking prior consent from the patients with clinical suspicion.

MEN syndrome was diagnosed based on the presence of two of the three major MEN-associated tumors viz. PHPT, entero-pancreatic neuroendocrine tumor, and pituitary tumor for MEN-1 and medullary thyroid carcinoma and pheochromocytoma for MEN-2A.

MEN-1 syndrome was also diagnosed in patients with any single major component of MEN-1 syndrome and the presence of a MEN-1 gene germline mutation [13]. All relatives of MEN-1 probands who consented were screened for the presence of MEN-1 syndrome.

Persistent hypercalcemia was defined as elevated calcium level with in six months of parathyroidectomy and recurrent hypercalcemia was defined as elevation of calcium level beyond six months of parathyroidectomy after initial postoperative normalization of calcium level [14].

Hormone analysis

All hormonal analysis was done by ECLIA (ELECSYS-2010, Roche Diagnostics, Germany model number Cobas e 411). The detection limit for PTH of this system was 1.20-5000 pg/ml, with a normal reference range of 15-65 pg/ml, and the cv was 6.5%. For 25OHD detection limit was 3-70 ng/ml, less than 20 ng/ml was considered a deficiency, and 21 ng/ml to 29 ng/ml was considered insufficiency. CV for 25OHD was 7.8%. Normal reference ranges for calcium and phosphate were 8.8 -10.2 mg/dl and 2.7 - 4.5 mg/dl respectively.

Statistical analysis

All analyses were conducted by using the Statistical Package for Social Sciences (version 21.0). The normality of data was assessed by the Shapiro-Wilk test. Upon determination of normality descriptive statistics in the form of mean, or median were presented accordingly. A comparison of two continuous variables was done by the student's T-test and Mann-Whitney U-test for normally and non-normally distributed data respectively. For the categorical variable, a chi-square test was performed. $P < 0.05$ was considered statistically significant.

Result

A cohort of 616 PHPT patients were registered in the electronic registry between 2012 and 2022. Among them, 72 (11.68%) were m-PHPT, remaining were s-PHPT. The mean age of s-PHPT patients was 43.4 ± 14.3 years, and m-PHPT was 35.8 ± 13.5 years ($p < 0.05$). Among the m-PHPT, 70 (97%) had MEN-1 syndrome and 2 had MEN-2A syndrome. Overall, a female preponderance was seen in both cohorts, with female to male ratio being 2.8: 1 and 1.5: 1 in s-PHPT and m-PHPT respectively. The most common presenting symptom for both s-PHPT and m-PHPT was diffuse musculoskeletal pain, followed by renal stone disease.

Both s-PHPT and m-PHPT had comparable mean serum calcium (11.9 ± 1.5 vs 11.9 ± 1.6 mg/dl), and phosphate (2.7 ± 1 vs 2.6 ± 0.7 mg/dl) at the time of presentation. Median PTH level was 314 pg/ml (IQR 161-984 pg/ml) and 292 pg/ml (IQR 180-818 pg/ml) at presentation in s-PHPT and m-PHPT respectively. Median 25OHD level was 19.3 ng/ml IQR 10.4-30.4 ng/ml and 15 ng/ml IQR 8.1 – 25.1 ng/ml ($p < 0.05$) for s-PHPT and m-PHPT respectively. Median tumor weight was higher in s-PHPT cases (2.5 gm; IQR 0.8-7.3 gm) compared to m-PHPT cases (1.9 gm; IQR 1.08-4.05 gm) as mentioned in Table 1.

The preoperative parathyroid gland localization by either ultrasonography (USG) of the neck and/or Sesta-MIBI scan was successful in 94% (n=511) patients in the s-PHPT cohort. Among s-PHPT patients left inferior parathyroid adenoma (LIPA) was the most common gland involved (220;40%), followed by a right inferior parathyroid adenoma (RIPA) in 34%. Multiglandular disease was present in 32 (6%) patients. Five patients had ectopic localization of the parathyroid tumor. The multiglandular disease was more common in m-PHPT (28, 40%) compared to sporadic

	s-PHPT (n-544)	m-PHPT (n-72)	p-value
Age (years)#	43.4 ± 14.3	35.8 ± 13.5	p < 0.05
Gender (F: M) *	2.8: 1	1.5:1	p > 0.05
Presenting symptoms			
Musculoskeletal pain *	347 (64%)	33(46%)	p < 0.05
Renal stone disease*	327 (60%)	27(38%)	p < 0.05
Pancreatitis*	90 (16%)	13(18%)	p > 0.05
Psychiatric issue*	95 (18%)	-	
Asymptomatic*	79 (14.5%)	19(26%)	p < 0.05
Other MEN component	-	29(40%)	
Biochemistry			
Baseline calcium (mean) (mg/dl) #	11.9 ± 1.5	11.9 ± 1.6	p > 0.05
Baseline phosphate (mean) (mg/dl) #	2.7 ± 1	2.58 ± 0.7	p > 0.05
Baseline PTH (median) (pg/ml) $	314 (IQR 161-984)	292 (IQR 180-818)	p > 0.05
Baseline 25OHD (ng/ml) $	19.3(IQR 10.430.4)	15(IQR 8.1 – 25.1)	p < 0.05
Multiglandular disease*	32 (6%)	28 (40%)	p < 0.05

Table 1: Demographic, symptomatology, presenting biochemical and localization characteristics of PHPT patients (N-616).

(* Chi-square test, # student t-test, $ Mann Whitney U test).

(s-PHPT: Sporadic Primary hyperparathyroidism, m-PHPT: Multiple endocrine neoplasia associated Primary hyperparathyroidism, F: Female, M: Male, 25OHD: 25 hydroxy vitamin D, MEN: Multiple endocrine neoplasia.

(The normal lab reference range of Calcium is 8.2-10.2 mg/dl, and Phosphate level is 2.5 -4.5 mg/dl, PTH 15-65 pg/ml, 25OHD 11-42 ng/ml).

cases (6%). USG of neck and sesta-MIBI scan concordance rate was 52% among s-PHPT cases (285 in 544 cases), whereas 68% (49 in 72 cases) m-PHPT cases.

Fifty patients underwent genetic analysis and rest 22 patients were diagnosed as per clinical criteria. Among patients who underwent genetic analysis (n-50) 48 of them had germline MEN-1 variant and the remaining 2 had germline *RET* mutation. The five most commonly encountered mutations associated with m-PHPT in this study were c.1838A>G, c.1817C>T, c.1525C>A, c.35A>T (5`untranslated region), and c.250C>T. *RET* mutations were present in two patients in codon c.634C>A and c.618C>P.

Among m-PHPT cases, 66 (90%) were index cases at the time of presentation, and the rest were detected on screening of family members of confirmed MEN-1 patients. Patients with s-PHPT compared to m-PHPT had more median post-surgery fall in PTH (84.81% vs 46.7%) and serum calcium (23.4% vs 16.59%) (p-value <0.05) respectively. Persistent hypercalcemia following surgery was reported in 20 (3.7%) patients with s-PHPT, whereas 8 patients (12%) had persistent hypercalcemia in m-PHPT patients. Recurrence of hypercalcemia was seen in 23 patients (4%) and 7 patients (9.8%) with s-PHPT and m-PHPT respectively as shown in Table 2.

	s-PHPT (n-544)	m-PHPT (n-72)	p-value
Post-operative reduction of serum calcium from baseline (median percentage) #	23.4%	16.59%	$p < 0.05$
Post-operative reduction of PTH from baseline (median percentage) #	84.81%	46.7%	$p < 0.05$
Persistent hypercalcemia*	20 (3.7%)	8 (12%)	$p < 0.05$
Recurrent hypercalcemia*	12 (2%)	7 (9.8%)	$p < 0.05$

Table 2: Comparison between s-PHPT and m-PHPT in terms and post-operative biochemical characteristics (n-616).

(# Mann Whitney U test, * Chi-square test.).

(s-PHPT: Sporadic Primary hyperparathyroidism, m-PHPT: Multiple endocrine neoplasia associated Primary hyperparathyroidism.).

Discussion

This study showed that m-PHPT had a younger age at presentation with no significant gender difference. The asymptomatic presentation was more common in m-PHPT as compared to its sporadic counterpart (26% vs 14.5%). Biochemically, except 25OHD level, all other parameters viz. calcium, phosphate, and PTH were almost comparable between these two cohorts at presentation. Sesta-MIBI scan and ultrasonography concordance rate was 68% in m-PHPT patients which was higher as compared to s-PHPT patients (52%). Multiglandular disease was significantly higher in m-PHPT compared to s-PHPT cases (40% vs 6%). Post-surgery median percentage fall of calcium and PTH were more in s-PHPT cases as compared to m-PHPT. Persistent hypercalcemia and recurrent hypercalcemia were more common in m-PHPT than in s-PHPT patients.

Demography of s-PHPT vs m-PHPT

The present study showed the mean age at presentation in the m-PHPT cohort was 35.8 ±13.5 years and in s-PHPT was 43.4 ± 14.3 years which was comparable to the study showing the largest reported cohort from the Netherlands, which showed younger age at the presentation in m-PHPT as compared to s-PHPT patients with a median age of 33 years (11-62) years and 63 years (20-88) years respectively [14]. An optimum age cut-off to consider m-PHPT among all PHPT cases was 37 years, any age below 37 years was associated with m-PHPT with a sensitivity of 71% and specificity of 67% in this cohort as shown in Figure 1.

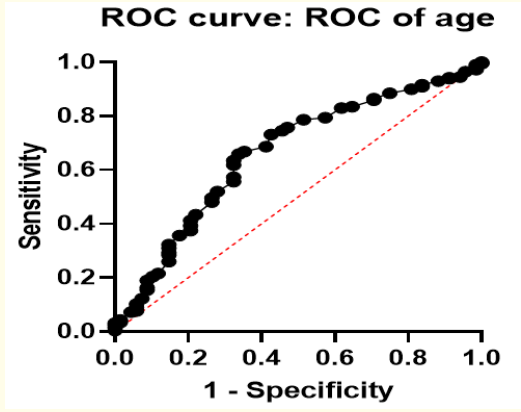

Figure 1: ROC curve showing age cut off from diagnosis of m-PHPT in comparison with s-PHPT. Optimum age cut off to m-PHPT case was 37 years, any age below 37 years were suggestive of m-PHPT with a sensitivity of 71% and specificity of 67%.

In this present study, the female-to-male ratio was 2.8:1 and 1.5:1 in s-PHPT and m-PHPT respectively. Two similar studies one from the Netherlands and another from Italy showed a comparable female preponderance [14,15]. An Indian study also showed similar observation as per as age of presentation and gender distribution is concerned [16].

Clinical and biochemical parameters of m-PHPT vs s-PHPT

The most common presenting complaints were diffuse skeletal pain followed by renal stone disease and pancreatitis in both

cohorts, but a relatively more percentage of patients presented with such complaints in s-PHPT as compared to m-PHPT ($p < 0.05$). The asymptomatic presentation was more common in m-PHPT than s-PHPT ($p < 0.05$,) as many of them picked up on preferential screening due to family history or due to other MEN-related tumors. Partially agreeing with these findings, some other studies showed similar observations, viz. fatigue, renal stone disease, and neuropsychiatric presentation as presenting complaints of PHPT [14,17].

The present study did not show any difference in serum calcium, phosphate, and PTH level among s-PHPT and m-PHPT patients. In a study by Cristina Eller-Vainicher and group showed a significant difference in PTH levels among s-PHPT and m-PHPT patients with s-PHPT had significantly higher PTH levels compared to m-PHPT counterparts, although calcium levels were comparable [15]. This contradictory finding viz. comparable calcium with low PTH among m-PHPT patients was also evident in a study from the Netherlands [14]. 25OHD was significantly low in m-PHPT patients than s-PHPT patients in the present study whereas the study by Cristina Eller-Vainicher and the group showed no such difference [15]. Five patients had normocalcemic PHPT in the m-PHPT cohort. This present study contradicts some of the prior studies showing the predictive value of PTH and calcium for diagnosing m-PHPT or s-PHPT. Similarly, another Indian study showed no difference in serum calcium, phosphate, parathyroid hormone, and 25OHD levels among different age groups although they have not assessed differences across s-PHPT and m-PHPT patients [18].

A total of 50 patients underwent genetic study, and 48 of them were positive for MEN-1-associated germline mutation and 2 had pathogenic RET mutation. The most common MEN-1 mutation encountered was in chromosome 11, and the mutation was c.35A>T which was like other studies [19,20].

Localization characteristics and surgical strategy of s-PHPT vs m-PHPT

Multiglandular disease was more common in m-PHPT than s-PHPT cases ($p < 0.05$). Among s-PHPT cases, most of the involved glands were from the left inferior parathyroid gland and this finding was like the observation made by another similar study [14]. Overall localizations were possible in 94% of patients in s-PHPT group which was like another Indian study that showed a localization accuracy of 93% after combining both USG and sesta-MIBI [16]. A relatively more percentage of cases showed ultrasonography and sesta-MIBI scan concordance in lesion(s) localization in the m-PHPT cohort compared to the s-PHPT cohort. More than one gland resection and bilateral exploration were done in m-PHPT compared to s-PHPT patients despite precise and concordant localization of disease signify true multiglandular involvement in m-PHPT patients.

Outcome characteristics of s-PHPT vs m-PHPT

As per as the fall of serum calcium and PTH were concerned, s-PHPT showed a greater reduction than m-PHPT with a median percent fall of 23% vs 16% and 84% vs 46% in s-PHPT and m-PHPT respectively. Greater number of patients presented with persistent and recurrent disease after the first surgery in m-PHPT compared to s-PHPT. Cumulative percentages of persistent and recurrent disease among s-PHPT and m-PHPT were 3.7% and 2% vs 12% and 9.7% respectively. These findings were similar to other study focusing on post-operative outcomes of PHPT patients [14]. Even after 3 gland removal in m-PHPT patients, quiet a few of them had persistent hypercalcemia, thereby explaining the theory of 4 gland hyperplasia in such a background. Since, auto transplantation outcome was not successful in some of the older series and even in this institute, and sustaining life with hypoparathyroidism and its consequences was far more detrimental than mild hypercalcemia secondary to single gland hyperplasia, 4 gland removal has not been tried in m-PHPT cohort in last 10 years [21].

Strength and limitations of the study

This study described the largest cohort of patients from India. A significant number of patients has undergone mutation study based on clinical suspicion. Being the highest referral center in northwest India, it has a representation of a larger population as well. Study has limitations like retrospective nature of the study and the referral bias.

Conclusion

This study showed that m-PHPT patients presented at an early age and had more asymptomatic presentation and multiglandular disease without significant difference in serum biochemistry,

whereas the percent fall in PTH and calcium were more in s-PHPT patients in the post-surgery period with less incidence of recurrent and persistent disease. The most encountered MEN-1 mutation was C.35A>T (5`untranslated region).

Ethical Statement

This study was ethically approved by the Institute Ethics Committee, PGIMER Chandigarh vide reference number NK/499/Res/1150. None of the authors had any conflict of interest. Though the study comprises data from human subjects analyzed retrospectively, prior to investigations such as genetic study, informed consent has been obtained from all the participants.

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