

Five-year Retrospective Study on Primary Hyperparathyroidism in South India: Emerging Roles of Minimally Invasive Parathyroidectomy and Preoperative Localization with Methionine Positron Emission Tomography-Computed Tomography Scan

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Abstract

Background: Primary hyperparathyroidism (PHPT) is a common endocrine disease with a variable clinical presentation. PHPT is usually symptomatic at presentation in majority of the patients, especially in developing countries. As the accessibility to investigations, advanced imaging methods and surgical procedures are improving, the clinical profile of the patients with PHPT has undergone a palpable change compared to the earlier description. Hence we decided to look for a change in clinical, imaging and surgical outcomes of PHPT patients from South India. **Methods:** We collected the data on clinical presentation, biochemistry, radiological features and operative findings of patients with PHPT treated in our hospital from 2011-2015. Cases of PHPT were identified from the laboratory values using the biochemical criteria, after the exclusion of secondary and tertiary hyperparathyroidism cases. **Results:** Our study identified 54 patients (19 males and 35 females) with age ranging from 16 to 71 years. A Significant proportion (38.9%) of the patients were asymptomatic. Musculoskeletal symptoms (40.7%), renal manifestations (27.7%) and gastrointestinal system involvement (27.7%) constituted the other common modes of presentation. CNS involvement was seen in 3 patients. A palpable nodule in the neck was detected in 4 patients. Interestingly 4 patients were managed for parathyroid crisis at presentation. Biochemical features included hypercalcaemia (100%) and hypophosphatemia (59%) with a mean intact PTH level of 602.0 ± 721.3 pg/ml. Sensitivity of Ultrasonography and Tc99M Sestamibi was 72% and 70.6% respectively for detecting a parathyroid adenoma. Sensitivity of C11 methionine PET-CT was 71.4% in those patients who were negative for other imaging modalities. Forty three patients (79.6%) underwent minimally invasive parathyroidectomy. **Conclusion:** In South India we have a notable change in the clinical presentation of PHPT from a symptomatic to an asymptomatic state. C11 Methionine PET - CT is an emerging modality for preoperative localisation especially when other imaging modalities are negative and when a minimally invasive parathyroidectomy is desired.

Keywords: C11 METHIONINE positron emission tomography-computed tomography, minimal access surgery, parathyroid gland weight, ^{99m}Tc sestamibi, Vitamin D

INTRODUCTION

Primary hyperparathyroidism is a relatively common endocrine disorder, with incidence as high as 1 in 500 to 1 in 1000.^[1] Hyperparathyroidism results from an increased and abnormal secretion of parathyroid hormone (PTH) from one or more of the four parathyroid glands. In 90% of the cases, hypercalcaemia is due to hyperparathyroidism or malignancy.^[2]

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Other possible causes of elevated calcium should be considered after excluding the above causes. Though hyperparathyroidism was initially considered as a rare disorder, the incidence has increased by 4–5 fold coinciding with the availability of multichannel biochemistry autoanalyzer.^[3]

Women are affected more often than men by a ratio of 3:1. Even though the disease can present at any age, majority of the patients are postmenopausal women.^[2,4] Parathyroid adenoma accounts for 80%–85% of primary hyperparathyroidism cases whereas parathyroid carcinoma is very rare and constitutes < 1% of cases.^[5] When primary hyperparathyroidism is diagnosed in childhood, it is important to consider the possibility of a genetic etiology such as Multiple Endocrine Neoplasia Type 1 and Multiple Endocrine Neoplasia Type 2.

Classical hyperparathyroidism is usually associated with a typical skeletal disorder, nephrolithiasis, and neuromuscular complaints. However, currently, many patients present without these symptoms and some of these patients are usually detected early in the course of the disease.^[6]

PATIENT AND METHODS

Our study was conducted at St. John's National Academy of Health Sciences, Bengaluru. All patients who underwent parathyroid surgery between January 2011 and December 2015 were included in this study. Patients were diagnosed as having hyperparathyroidism based on the following criteria.

- Elevated serum calcium level of >10.5 mg/dl (measured by modified ortho-cresolphthalein complexone method), and an inappropriately low phosphorous level (measured by modified phosphomolybdate method)
- Inappropriately high intact PTH (iPTH) measured by electrochemiluminescence sandwich assay with analytical sensitivity of 1.2 pg/ml.

In two patients, PTH values were not available from the review of charts. However, based on operative and histological findings along with biochemical and symptomatic resolution post parathyroid adenoma resection, they were also considered to be having primary hyperparathyroidism (PHPT).

24-h urinary calcium was measured by modified ortho-cresolphthalein complexone method. Urine was collected in a container containing 10–20 ml of 6 N (M) HCl.

25(OH) D was measured by competitive immunoassay (ADVIA Centaur XP system seimens healthcare diagnostics, analytical sensitivity 4.2 ng/ml).

Medical records of these patients were retrospectively reviewed for age, sex, previous medical history, presenting symptoms and signs, routine biochemical investigations, and histopathological diagnosis. Secondary and tertiary hyperparathyroidism cases were excluded. Preoperative localization studies included one or more of the following modalities namely ultrasonography (USG) using high-frequency (10–12 hertz)

linear probe, computed tomography (CT)/magnetic resonance imaging (MRI) scan, and ^{99m}Tc sestamibi scan. If these imaging modalities could not localize the adenoma, then a methionine positron emission tomography (PET)-CT was carried out to localize the same in patients desiring full localization prior to surgery. If the adenoma was localized, the patients were offered a minimally invasive parathyroidectomy. Minimally invasive parathyroidectomy is a surgical process which allows the surgeon to perform a traditional operation through an access that minimizes the trauma of surgical exposure and dissection. In other patients, neck exploration under general anesthesia with parathyroidectomy was carried out.

Statistical analysis

SPSS 17 (Statistical Package for Social Sciences 17, 2008, SPSS Inc, South Wacker Drive, Chicago, USA) was used for data analysis. The data are expressed as mean ± standard deviation; data that did not have a normal distribution are also expressed as median (range). Student's *t*-test or Mann–Whitney U-test (skewed data) was applied for comparing two groups. *P* ≤ 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the patients are described in Table 1. Thirty-five females (64.8%) and 19 males (35.2%) were included in this study. Mean age was 48.1 ± 15.8 years (males 46 ± 16.9 years and females 49.5 ± 14.2 years). Out of all patients, one patient was below 20 years of age, 32% of patients were between 20 and 40 years of age, and 66% were above 40 years of age.

On analysis of the clinical presentation [Figure 1] of patients, it was observed that 21 (38.9%) patients were completely asymptomatic. Fifteen (27.7%) patients presented with gastrointestinal symptoms and 4 (7.4%) had acute pancreatitis at presentation. With respect to the renal manifestations, it was observed that 15 patients (27.7%) out of the whole cohort had renal involvement. Renal calculus was observed in ten patients (18.5%) while three had pyelonephritis (5.5%) and three patients had medullary nephrocalcinosis (5.5%). In addition, 22 (40.7%) patients presented with musculoskeletal symptoms predominantly in the form of bone pains (*n* = 18, 33.3%), proximal myopathy (*n* = 2, 3.7%), and fractures (*n* = 2, 3.7%). In our series, three (5.5%) patients

Table 1: Clinical characteristics of 54 patients with hyperparathyroidism

Presenting symptoms	Number of patients (%)
Asymptomatic	21 (38.9)
Musculoskeletal manifestations (bone pain, weakness)	22 (40.7)
Gastrointestinal manifestations (anorexia, vomiting, and constipation)	15 (27.7)
Renal manifestations (renal stones, pyelonephritis)	15 (27.7)
CNS manifestations (encephalopathy, seizure)	5 (9.2)

CNS: Central nervous system

had central nervous system (CNS) involvement in the form of psychiatric disturbances ($n = 2$) and encephalopathy ($n = 1$) as the initial presenting feature [Figure 2]. In fact, in the 21 (38.9%) asymptomatic patients, hypercalcemia was an incidental finding during routine biochemical testing. Four patients had a palpable parathyroid mass during clinical examination. Four patients (7.4%) had parathyroid crisis at presentation to hospital and three patients underwent hemodialysis to reduce serum calcium levels before parathyroid surgery.

Average serum calcium, phosphorous, 25(OH) D, and iPTH levels were $12.7 (\pm 2.04)$ mg/dl, $2.4 (\pm 0.7)$ mg/dl, $11.34 (\pm 12)$ ng/ml, and $602 (\pm 721)$ pg/ml, respectively [Table 2]. Average total alkaline phosphatase level in this cohort of patients with PHPT was $375.5 (\pm 69.71)$ IU/L.

There was a statistically significant association between the serum calcium and PTH when PTH levels were >600 pg/ml using Student's *t*-test [Table 3]. A positive trend was also noticed between parathyroid gland weight and PTH when PTH levels were >600 pg/ml. However, there was no significant association between 24-h urinary calcium levels and PTH levels in our study. Serum alkaline phosphatase levels were also significantly higher with higher PTH levels.

There was no significant association between the serum calcium and 25(OH) D levels or between PTH and 25(OH)D. However, as 25(OH) D levels decreased, there was an associated increase in PTH and calcium levels and the same was not statistically significant [Figure 3].

At surgery and later on with histology, majority (91%) of the patients were found to have a parathyroid adenoma. Four patients had hyperplasia of all glands and one patient had a parathyroid carcinoma. Mean parathyroid gland weight was $4.94 (\pm 1.54)$ g.

Preoperative imaging [Table 4] was done in all patients for localization. The imaging modalities included USG (100% of patients), ^{99m}Tc sestamibi (62.3% of patients), C-11 methionine PET-CT (13.5% of patients) [Figure 4], and CT neck (3.3% of patients). USG showed a sensitivity of 72.2% for localizing

adenoma with a positive predictive value of 95.12%. The sensitivity of ^{99m}Tc -Sestamibi was 70.6% with a positive predictive value of 96%. The true positivity rate for C-11 methionine PET-CT was 71.4% in patients who were negative for USG and ^{99m}Tc -sestamibi [Table 4].

In our study, 43 patients (79.6%) underwent minimally invasive parathyroidectomy. Among these patients, 27 procedures were done under local anesthesia (cervical block $n = 4$, local anesthesia only $n = 23$), five under monitored anesthesia care, and 10 under general anesthesia. One patient had

Table 2: Biochemical parameters of patients with primary hyperparathyroidism

Biochemical parameters	Mean \pm SD
Serum calcium (mg/dl)	12.7 \pm 2.04
Serum phosphorus (mg/dl)	2.43 \pm 0.7
Serum parathyroid (pg/ml)	602.6 \pm 721
25-(OH) D (11.34 ng/ml)	11.34 \pm 9
Serum alkaline phosphatase (IU/L)	375.5 \pm 314
24 h urinary calcium (mg/24 h)	332 \pm 124

25-(OH) D: 25-hydroxy Vitamin D, SD: Standard deviation

Table 3: Relation between parathyroid hormone, calcium, parathyroid gland weight, and 24-h urine calcium

	PTH	n	Mean \pm SD	Significant (two tailed)
Calcium (8.5-10.5 mg/dl)	<600	36	11.93 \pm 1.62	0.003
	>600	16	13.69 \pm 2.47	0.016
Gland weight (g)	<600	20	2.42 \pm 2.39	0.017
	>600	13	9.02 \pm 11.31	0.061
24-h urine calcium (mg/24 h)	<600	20	286.92 \pm 177.59	0.981
	>600	6	288.75 \pm 95.43	0.974

SD: Standard deviation, PTH: Parathyroid hormone

Table 4: Imaging characteristics of parathyroid adenoma

Imaging (number of patients)	True positive (%)	False negative (%)
Ultrasonography (54)	72.2	27.8
^{99m}Tc sestamibi scan (34)	70.6	29.4
C-11 methionine PET-CT (8)	71.4	28.6

PET: Positron emission tomography, CT: Computed tomography

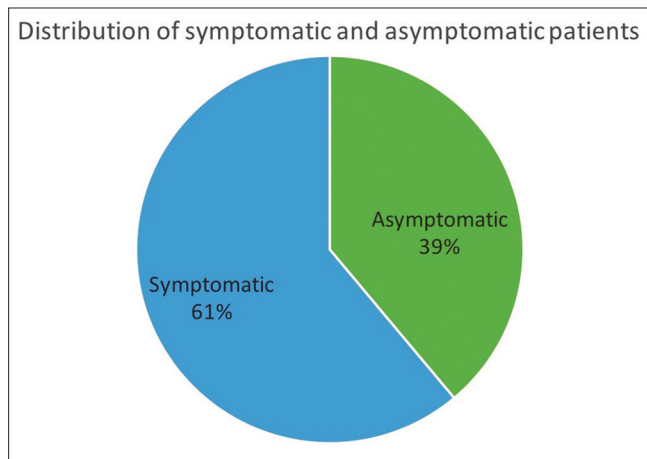


Figure 1: Percentage distribution of symptomatic and asymptomatic primary hyperparathyroidism

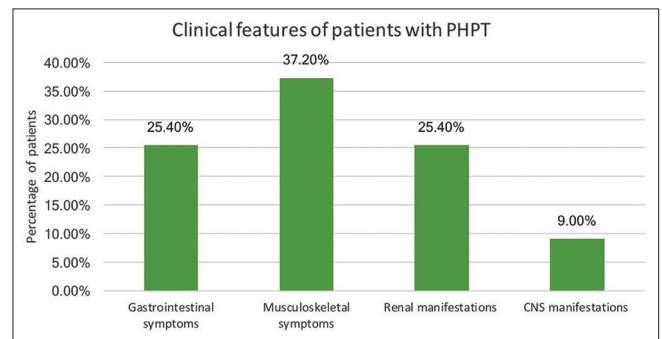


Figure 2: Clinical feature of patients with primary hyperparathyroidism

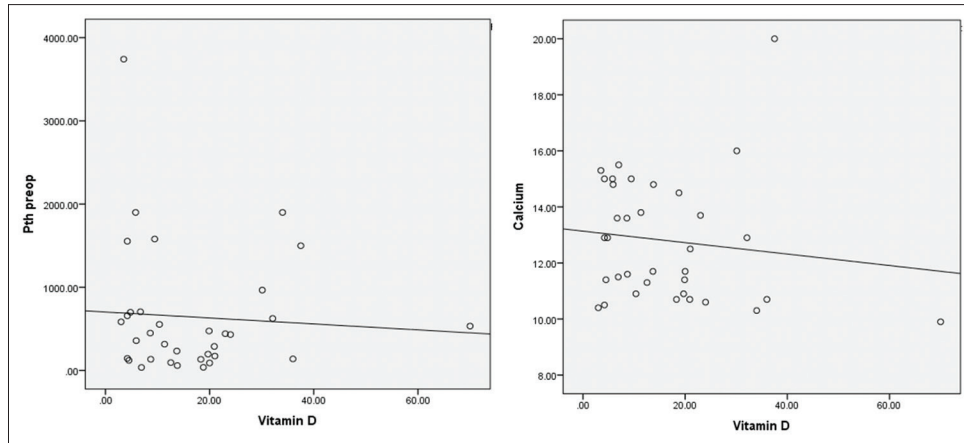


Figure 3: Relationship between calcium, parathyroid hormone, and 25(OH)D

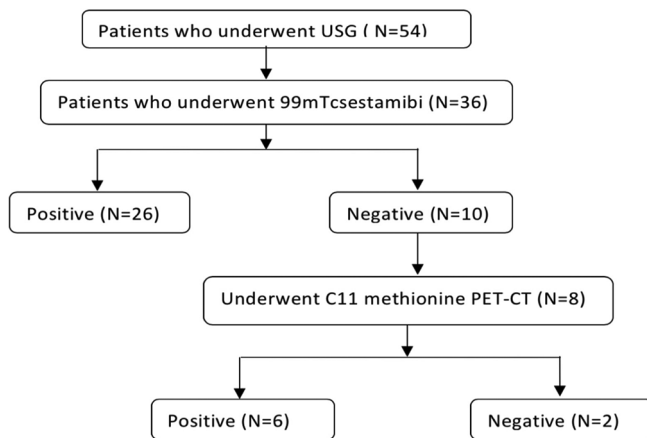


Figure 4: Preoperative imaging characteristics of primary hyperparathyroidism

local anesthesia converted to general anesthesia due to false-positive imaging with C-11 methionine PET-CT. About 60% of patients developed features of hypocalcemia postoperatively and were treated symptomatically. All cases of hypocalcemia were temporary and no one developed permanent hypoparathyroidism.

DISCUSSION

PTH and 25(OH) D play an important role in the homeostasis of calcium, phosphorous, and bone. PHPT is a common endocrine condition.^[7-9] Many patients with PHPT are asymptomatic, and mild symptoms may not initiate steps toward the diagnosis of primary hyperparathyroidism. However, in developing countries, symptomatic presentation is still commonly seen.^[10] In India, we do not have clear data on the prevalence of asymptomatic hyperparathyroidism, as screening for this condition is not done routinely. However, in a study by Mithal *et al.* from North India, 38% of patients were asymptomatic and our data are in agreement with their study.^[11] Our study revealed some unique findings. In our study, 38.9% of patients were asymptomatic and we used 11C methionine PET scan for identifying adenoma

in patients who did not localize the adenoma by USG and ^{99m}Tc sestamibi scan. Furthermore, a significant number of patients underwent minimally invasive parathyroidectomy after localization of the adenoma. A study by Shah *et al.*^[12] looked at a subgroup of patients presented between 2000 and 2010. In this study, the presenting features of the patients were musculoskeletal symptoms (skeletal deformities, bone pains, etc., in 53.4%) gastrointestinal symptoms, (constipation [36%], vomiting [29%], pancreatitis [17.5%]), and genitourinary symptoms (renal stones [41%] and hematuria [7.5%]).^[12] In another study from North India by Bhansali *et al.*, cardiac (hypertension, etc.) and CNS (anxiety, palpitation, arrhythmias, encephalopathy, etc.) manifestations were found in 42% and 23% of PHPT patients, respectively.^[13]

Mean age of the patients in our study was 48.1 years, indicating that our patients presented early compared to patients in developed countries where the mean age of presentation was between 55 and 62 years.^[14,15] Our study is not in agreement with the results of other Indian studies where majority of patients were <40 years of age.^[16-18] In one study from Kashmir, the mean age of patients at presentation was 44.72 ± 12.46 years which matches with our data probably because 62% of patients in that study were enrolled after 2012.^[19] The reason why PHPT presents at a younger age in our country is possibly because of the associated Vitamin D deficiency. However, in the study from Kashmir, the mean 25(OH) D levels were surprisingly good. However, our study is in agreement with the subgroup of patients from AIIMS, New Delhi, in the Indian Parathyroid Registry data, who had a mean 25(OH) D level of $11.9 (\pm 10.1)$ ng/ml.^[11] A significant reason for morbidity with PHPT is due to skeletal manifestations. In our study, 40.7% of patients had musculoskeletal involvement as a presenting symptom. Nutritional status of the patients along with calcium stores and 25(OH) D levels determines the severity of bone involvement in PHPT.^[20] A study from India did not find any difference in clinical manifestations between 25(OH) D-sufficient and 25(OH) D-deficient population.^[21] In a nutritionally sufficient population and in places where routine biochemical evaluation of calcium is common, symptomatic PHPT and clinical manifestations such

as osteitis fibrosa cystica (OFC) are rarely seen. In our series, we had only one patient who presented with OFC.

Renal involvement in the form of renal stones, impaired renal function, and pyelonephritis was present in 27.7% of our patients and 10 (18.5%) of our patients had only renal stones as the initial presentation. This is in contrast with the studies done in other parts of India where renal stones were present in up to 65%–70% of patients as part of initial presentation.^[16,19] Our data are similar to the data from developed countries where the initial presentation with renal stones has receded in the recent years and more asymptomatic cases are detected.^[22,23] This finding could probably be explained as we had a significant number of asymptomatic patients and our cohort of patients probably underwent routine biochemical evaluation more frequently than people from other parts of India.

Gastrointestinal involvement in the form of abdominal pain, anorexia, vomiting, and constipation was present in 27.7% of the patients. Only four (7.4%) patients presented with features of pancreatitis as the initial manifestation of PHPT. Prevalence of pancreatitis secondary to hyperparathyroidism was found to be higher in Indian patients and is described in 11%–13% of PHPT patients.^[24] Probable mechanisms of pancreatitis include hypercalcemia-induced activation of trypsinogen to trypsin, ductal obstruction due to pancreatic calculi, and genetic risk factors.^[19] There are case reports of recurrent episodes of pancreatitis in patients with PHPT.^[25] In a Indian study which looked at the gastrointestinal manifestations of PHPT, abdominal pain (43%) was the most common presenting feature followed by constipation (36%) and nausea (22%), and in the same study, 22% of patients had a history of gall stones with an increased incidence of pancreatitis in men and gallstone disease in women.^[26] The difference in symptomatology compared to our study population is probably because of early presentation in our cohort and different population characteristics.

In our study, hypercalcemia was found in all patients, but it was present in only 87% of patients in a study from North India by Bhansali *et al.*^[13] In our series, 59% of patients with PHPT had hypophosphatemia (<2.5 mg/dl), and this is in agreement with data from other Indian studies where it was present in 65.4% and 69% of patients, respectively, in studies by Bhansali *et al.*^[13] and Misgar *et al.*^[19] The mean phosphorous level in our study was 2.43 ± 0.7 mg/dl which was slightly lesser than the mean phosphorous level of 2.8 ± 0.9 mg/dL in the Indian Parathyroid Registry.^[16]

In this study, we found that there was a significant association of preoperative PTH level with the weight of the parathyroid gland and serum calcium levels but not with 24-h urinary calcium levels. Calcium levels and gland weight were higher and statistically significant when PTH levels were > 600 pg/ml. We did not find any association between gland weight and serum 25(OH) D levels. Around 59.3% of patients in our study had elevated alkaline phosphatase level which is in agreement with the studies done in North India.^[18]

Due to their embryological development, parathyroids are known to vary in their location, and preoperative localization of the adenoma may be helpful prior to the surgery. Parathyroid glands may be located in the retro-esophageal space, lateral neck, or in the mediastinum, which are the typical ectopic sites.

Noninvasive imaging of the patients with PHPT includes the use of USG, CT, MRI, ^{99m}Tc sestamibi [Figure 5], and thallium-technetium subtraction studies. More recently, C-11 methionine [Figure 6] uptake PET-CT is being used. C-11-methionine uptake mechanism is not yet fully understood but it is presumed to be involved in the synthesis of pre-pro-PTH, a PTH precursor, which results in intense and specific uptake in hyperfunctioning parathyroid glands.^[27,28] Scintigraphy studies have an advantage over other imaging modalities as they can identify ectopic parathyroid gland situated in mediastinum and cervical region simultaneously.

We used the imaging modalities for preoperative localization depending on the affordability and clinical situation of the patient. However, USG was done in all patients. In our series, USG and TC-99 m had almost similar sensitivity and positive predictive value. Some studies have reported better sensitivity and specificity (91%–100%) for ^{99m}Tc sestamibi scan.^[29,30] In an Indian study, the sensitivity and positive predictive value of USG were 73% and 95%, respectively. The sensitivity and positive predictive value were 98% for ^{99m}Tc sestamibi scintigraphy.^[31] In other studies, sensitivity of 91.7% for C-11 methionine PET-CT has been reported,^[29] but in our series, sensitivity of PET-CT was 71.4% with positive predictive value of 83.8%, probably because it was done in patients who were negative for USG and Tc-99 mSestamibi scan. In our study, only eight patients (13.5%) underwent C-11 methionine uptake PET-CT. Among them, two patients had a possibility of parathyroid adenoma on USG, but did not show uptake in ^{99m}Tc sestamibi scan and the remaining six patients were negative on imaging for parathyroid adenoma both on USG and Sestamibi. This underscores the importance of C-11 methionine PET-CT in those patients who were negative on other imaging modalities for PHPT. However, in two patients, even C-11 methionine PET-CT could not identify the parathyroid lesion and they underwent explorative parathyroidectomy.



Figure 5: ^{99m}Tc sestamibi scan showing adenoma



Figure 6: C-11 methionine positron emission tomography-computed tomography showing adenoma

Surgery is the only curative treatment for patients with PHPT. Four-gland exploration was long considered as the gold standard surgical approach and it remains the procedure of choice in patients with no suggestive localization studies.^[4] With the availability of various imaging techniques, nowadays, it is possible to subject the patient to minimally invasive parathyroidectomy.^[32,33] Although many patients developed hypocalcemia, it was not difficult to manage, and only a few (13%) patients required intravenous calcium correction and none of them had permanent hypoparathyroidism.

In the last decade, we have had some excellent publications on hyperparathyroidism from the Indian subcontinent. However, there are a few lacunae to be addressed. Data from the southern part of India are less and we felt that this population has to be represented. Our population has a right mix of urban and rural representation. In many urban middle-class people, hypercalcemia is detected during routine biochemical screening and they are asymptomatic. To date, as far as the Indian data are concerned, most of the studies have described that the presentation of PHPT patients is symptomatic, and in our study, ~39% were completely asymptomatic. We also had a good experience on preoperative localization with C-11 methionine PET-CT and the data on the same are rare in other studies from India. There was a shift in our operative technique and we started minimally invasive parathyroidectomy with a significant number of surgeries being done under local anesthesia also. Since the data on minimally invasive parathyroidectomy from South India are less, we have decided to present the same in this article. We considered these to be a useful addition to the data that exist. Moreover, as more minimally invasive parathyroidectomies are being done, preoperative localization may be demanding and our article shows the way in this aspect.

Limitations of this study were that some laboratory values (24-h urinary calcium, 25(OH) D, and weight of the gland) were not available for all the patients, genetic screening for MEN1 and MEN2 was not done, and weight of the gland was

not available in all the patients. Socioeconomic status of the patients was not evaluated.

CONCLUSION

In South India, we have a notable change in clinical presentation of PHPT from a symptomatic to an asymptomatic state. C-11 methionine PET-CT is an emerging modality for preoperative localization, especially when other imaging modalities are negative and a minimally invasive parathyroidectomy is desired.

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Conflicts of interest

There are no conflicts of interest.

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