Original Article

Primary hyperparathyroidism: A changing scenario in India

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ABSTRACT

Introduction: Primary hyperparathyroidism (PHPT) is largely a symptomatic disease with varied systemic manifestations, complicated by coexisting Vitamin D (Vit D) deficiency. Increasing awareness, developments in diagnostics, and Vit D supplementation may have an impact on the disease profile of PHPT. **Methods:** Clinical, biochemical, and pathological profile of PHPT presenting to a tertiary care center in South India were compared in two groups separated as per the period of presentation (Group A: January 1994–May 2007 - 51 cases and Group B: June 2007–January 2015 - 59 cases). **Results:** PHPT has remained a disease of female preponderance with similar age of presentation. It is being diagnosed earlier (mean duration of symptoms prior to diagnosis was 38.7 months in Group A, significantly longer than 26 months in Group B). Bone pain and metabolic myopathy were the most common presentations (60%) followed by pathological fracture (16%), renal calculi (13%), and pancreatitis (7%). Pathological fractures have become less frequent. Vit D deficiency is still a widespread co-morbidity. Radionuclide scintigraphy is an effective localizing tool, but ultrasound can be an inexpensive and widely available screening modality. **Conclusion:** PHPT still remains asymptomatic disease of bones and stones, although it is being diagnosed early. Greater awareness, Vit D supplementation, and better diagnostic tools have made it a disease with lesser morbidity and effective cure.

Key words: Parathyroid adenoma, primary hyperparathyroidism, Vitamin D deficiency

Introduction

Primary hyperparathyroidism (PHPT) in India, unlike in the Western world, is largely asymptomatic disease. Due to lack of awareness and routine calcium estimation, delayed presentation and co-existing calcium and Vitamin D (Vit D) deficiency, bone and other systemic involvement are more commonly seen.[1] With greater awareness among physicians, widespread use of AutoAnalyzers, and increasing trend of Vit D supplementation, it is expected that the clinical and biochemical presentation of this entity is likely to change. Studies from North India have looked at this trend over the past.[2] Having studied the profile of PHPT from a single center in South India during the period January 1994–May 2007, we collected data for the cases of PHPT presenting after this period until January 2015 and compared these two groups for changing trends.

Methods

We retrospectively studied patients with PHPT treated at a single center in South India between January 1994 and

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January 2015. This period was divided into two blocks: January 1994 to May 2007 (earlier reported by us) as Group A and from June 2007 to January 2015 as Group B for comparison.[3] Diagnosis of PHPT was established by the presence of raised serum intact parathormone (iPTH) with simultaneous raised corrected serum calcium. In cases with normocalcemia where there was a strong clinical and radiological suspicion of PHPT, Vit D supplementation with Vit D (cholecalciferol 60,000 IU granules), weekly for 6 weeks was given. Serum calcium and phosphate was repeated after 8 weeks to look for hypercalcemia. In cases with persistent normocalcemia, cause for secondary hyperparathyroidism was ruled out by relevant investigations. Workup for renal tubular acidosis (RTA) was done in patients with renal stones, hypokalemia, or fasting urine pH > 5.5. Plasma and urine pH, bicarbonate levels, and anion gap were tested in these patients. Distal RTA was diagnosed based on spontaneous or induced metabolic acidosis (ammonium chloride loading test) with simultaneous urine pH > 5.5. Biochemical assays were performed in fully automated biochemistry analyzer EM 360, manufactured by Transasia Biomedicals Ltd., Andheri East, Mumbai, Maharashtra, India, by methods as specified against each parameter, calcium (Arsenazo method), phosphate (ultraviolet phosphomolybdate, colorimetric without precipitation), alkaline phosphatase (modified IFCC), and albumin (biuret method). Serum 25OH Vit D and PTH levels were done by chemiluminescence assay (Cobas e411, Roche Diagnostics International Ltd, CH-6343 Rotkreuz, Switzerland). Inter- and intra-assay coefficient of variation (CV) for the hormone assays varied between 3–4.9% and 1.6–1.9%, respectively. Vit D assay during the Group A data acquisition was done by radioimmunoassay (RIA) in a fully automated RIA SR-300, manufactured by ABDIACHEM, New Delhi, India (inter- and intra-assay CV 3.8–6.2% and 1.6–3.1%, respectively). Localization of the culprit gland was done by ultrasonography (USG) and confirmed by technetium (Tc)-labeled sestamibi scan. Whenever the localization failed by these methods, computed tomography (CT) or magnetic resonance imaging (MRI) scan was done. Single photon emission CT scan was done in two cases, one with failed surgical exploration, and another with sestamibi positive scan but failed anatomical localization on USG. All patients underwent surgical resection of the culprit parathyroid gland lesion. Peroperative findings regarding parathyroid gland location, weight, and histopathology of glands were noted. Details regarding postoperative follow-up with clinical evaluation including tests for incipient hypoparathyroidism (Trousseau's and Chvostek's signs), serum calcium, inorganic phosphorus, and alkaline phosphatase were recorded. Normal serum calcium and iPTH after 1-month of surgery was taken as criteria of cure for PHPT. Statistical analyses were performed with relevant tests for significance of mean and frequency using SPSS Statistics Version 20 manufactured by IBM Inc. USA.

Results

A total of 110 (Group A – $n = 51$ and Group B – $n = 59$) consecutive cases of PHPT were studied [Table 1]. The gender distribution was 78 females and 32 males with 06 patients in the pediatric age group (age <18 year). Their mean age was 37.5 ± 11.2 (range 13–70 years). Mean duration of symptoms prior to diagnosis was 38.7 months in the former group and 26 months in the later. ($P < 0.001$) The most common site of adenoma was left inferior parathyroid followed by right inferior and then the superior glands [Table 2]. Relevant clinical, biochemical data and details of localization studies are tabulated in Tables 1-3 with comparison between the two groups. Tc-labeled sestamibi scan for parathyroid glands was performed in all the cases and was negative only in one patient, in whom the adenoma was localized by MRI scan. Fifty-seven out of the total of 59 patients in Group B underwent screening by USG, and 53 were detected positive (four glands in ectopic location failed localization) while all seven in the earlier period were positive.

All patients underwent surgical management with resection of the culprit gland. Weight of the resected glands varied from 0.3 g to 35 g (median 2.5 g) in Group B. Similar data were not collected in Group A. The duration of symptoms, in Group B, prior to diagnosis was longer in those with greater gland weight. It was mean 3.67 years (±1.23) in those with gland weight <2.5 g versus 6.33 years (±2.07) in those with gland weight >2.5 g ($P = 0.0034$).

All the cases responded well to surgical excision of the parathyroid lesion with normalization of calcium and iPTH levels. Radical neck dissection was done in three out of four cases of parathyroid carcinoma in whom the diagnosis of parathyroid carcinoma was suspected on clinical grounds and later confirmed on histopathology. The fourth case was diagnosed only on histopathology postoperatively. In the total eight cases of parathyroid hyperplasia, subtotal parathyroidectomy (3½ gland resection) was done. Hypocalcemia was noted in all patients with successful surgical excision, requiring IV calcium replacement for up to 48 h. Twenty-six cases required prolonged parenteral calcium replacement ranging from 3 to 7 days. All patients received 1.5 g of oral calcium supplementation with 0.25 mcg 1-alfacalcidol if severe hypocalcemia for nearly 3 months.

Table 1: Comparison of clinical, biochemical and radiological features of primary hyperparathyroidism compared between the two groups during the study period (Group A - Jan 1994 to May 2007 and Group B - Jun 2007 to Jan 2015)

	Group A (*N*=51)	Group B (*N*=59)	*P* value
Parameter			
Mean age (years)	39.5+11.5	37+10	0.22
Gender distribution (Male:Female)	17/34	15/44	0.29
Mean duration of illness (Prior to diagnosis) (months)	38.7+5.13	26+6.85	<0.001
Biochemical profile			
Hyper calcemia (*n*)	40	52	0.2
Raised ALP (*n*)	36	48	0.26
PTH (pg/ml) (Mean±SE)	732.3+146.9 (range 136-2066)	1153+338.7 (range 161-2834)	0.28
Low Vit D (%)	100	88	0.001
Clinical profile			
Bone pains/Myopathy	24 (4 - dRTA)	43 (2 - dRTA)	0.006
Pathological fractures	12	0	<0.0001
Bony swelling/deformity/rickets (children <18 year age)	03 (PTH >10x/ALP>5 × ULN)	03 (PTH >10x/ALP>5x ULN)	1.09
Renal stones (*n*)	7	7	0.78
Pancreatitis (*n*)	4	4	1.0
Others	1	2	
Skeletal involvement			
Brown tumors	19	7	0.003
Osteopenia	27	35	0.56
Normal	5	17	0.01

PTH: Parathyroid hormone, dRTA: distal Renal Tubular Acidosis, ALP: Alkaline phosphatase, ULN: Upper limit of normal

Table 2: Distribution of pathological characteristics in the cases of PHPT and their comparison between the two groups (Group A - Jan 1994 to May 2007 and Group B - Jun 2007 to Jan 2015)

	Group A (*N*=51)	Group B (*N*=59)	*P* value
Pathology			
Adenoma	44	54	0.5
Hyperplasia	4	4	1.0
Carcinoma	3	1	0.33
Location of adenoma			
Inferior parathyroid	41(L28, R13)	53(L34R19)	0.18
Superior parathyroid	3(L2, R1)	2(L1, R1)	0.67
Ectopic	7	4	0.34

A total of 97 patients were available for follow-up for a mean duration of 40 (±29.3) months (range – 3 months to 20 years). Biochemical assessment on follow-up revealed normal calcium, phosphorus, alkaline phosphatase (ALP), and iPTH levels. None of the patients in this study had a recurrence of PHPT during the period of follow-up.

Discussion

We retrospectively studied 110 consecutive patients with symptomatic PHPT presenting to a tertiary care center in South India during the period January 1994–January 2015 and comparatively studied the characteristics of these cases divided into two groups presenting from January 1994 to May 2007 (161 months), presented in our earlier publication on the subject and later from June 2007 to January 2015 (92 months).[3-6] We aimed to see the trends developing in the last two decades in disease profile of PHPT.

With the increase in awareness regarding this condition and availability of AutoAnalyzers, calcium estimation has become a frequently performed investigation in most centers. This helps in detecting asymptomatic hypercalcemia and those with minor or nonspecific symptoms. Protocols for the evaluation of pathological fractures, osteoporosis, renal stones, pancreatitis, and other complications of hypercalcemia and PHPT have further made the diagnosis of PHPT more frequent as seen in this study where more cases were picked up in the later part of the study. Diagnosis was made earlier in the later part of the study likely due to greater awareness among the clinicians and better diagnostic protocols.

Bone involvement was more severe with brown tumors and pathological fractures in Group A than in Group B, where osteopenic appearance of bones on plain radiographs or normal bones was more frequently seen.[3,5,6] This was likely due to early diagnosis and improvement in Vit D status in Group B. Children (<18 years) with PHPT presenting with associated Vit D deficiency had severe bone disease, deformities six patients in this series) which only partially recovered after the establishment of cure. Alkaline phosphatase and PTH levels in them were high, suggesting the impact of superimposed Vit D deficiency leading to deforming rickets.

During the period of study, there was no change in the age and gender distribution of the patients. The proportion of patients presenting with hypercalcemia and normocalcemia also did not show any change. Vit D deficiency was seen in significantly greater proportion of

Table 3: Localization techniques in PHPT

Localisation technique	GpA (done/positive)	GpB (done/positive)	Remarks
Tc 99m Sestamibi scan	38/38	59/58*	Positive predictive value 98%
Tetrafosmin scan	01/01	0	Sensitivity 99%
Thallium-Tc Substraction scan	12/12	0	
Ultrasonography	7/7*	57/53*	Positive predictive value 92%
		(4 Ectopic parathyroid glands – False negative scans)	Sensitivity 93%
CT scan	6/6*	3/3*	
MRI	0	1/1	Sestamibi negative
SPECT	0	2/2*	Failed anatomical localisation-1/ negative first exploration-1
		*Confirmed on Sestamibi scan and post-operatively	

PHPT: Primary hyperparathyroidism, MRI: Magnetic resonance imaging

patients in the earlier group, suggesting improvement in awareness regarding Vit D supplementation and its use in clinical practice. Raised ALP levels were seen more frequently, and PTH levels were higher in the later group, although not significant which was likely due to newer assays of PTH measurement.

Tc-labeled sestamibi scan for parathyroid glands was negative only in one patient (positive predictive value 98%, sensitivity 99%) in whom the adenoma was localized by MRI scan. This was likely due to the small size and ectopic location of the gland which made the localization by CT alone or by radioisotope scan difficult.[7,8] USG with 92% positive predictive value and sensitivity of 93% was noted to be a reliable and economically-effective modality for localizing the culprit parathyroid lesion.

Solitary parathyroid adenoma remained the most common cause of PHPT in both the groups with left inferior glands being affected more frequently as seen in another study from India.[2] Weight of the resected glands in Group B varied from 0.3 to 35 g (median 2.5 g). In the previous study from North India, mean weight of the adenoma was higher (4.7 g), and the mean duration of symptoms prior to diagnosis was 42–44 months, longer than that seen in our recent patients (26 months). This probably explains the greater gland weight seen in their study.[2,9]

With greater awareness, screening for PHPT in cases with bone and other systemic involvement suggestive of this uncommon condition, widespread Vit D supplementation and greater availability of multi-parameter AutoAnalyzers, it appears that PHPT will be seen more frequently and at an earlier stage of the disease. USG is an effective, inexpensive, and widely available tool for localizing the culprit gland after biochemical diagnosis is established. With early diagnosis and less severe skeletal involvement, the profile of PHPT has undergone a welcome change. Greater awareness will help in early detection and effective amelioration of various systemic complications including improvement of overall bone health.

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Conflicts of interest
There are no conflicts of interest.

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