

Original Research Article

Clinical profile of primary hyperparathyroidism in Northeast India: a single centre experience

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ABSTRACT

Background: A retrospective study of the presentation of primary hyperparathyroidism was done at a tertiary care centre in northeast India and was compared with variable features in other parts in India and worldwide.

Methods: The clinical presentation, biochemical parameters, radiological and histopathology findings of 27 subjects of primary hyperparathyroidism who presented to us over a period of 5 years were retrospectively analysed. Chi-square test, student t test and 'one way ANOVA' were used to compare different variables. Statistical significance was set at $p < 0.05$.

Results: The age distribution ranged from as young as 13 years to 72 years (39 ± 16.7). The male:female ratio was 1:1.25. The duration of symptoms at presentation ranged from 2 to 72 months (21.7 ± 20.3). The most common presentation was bone pain in 59.2% of cases, followed by proximal myopathy (48.1%), fatigue (44.4%), abdominal pain (44.4%), constipation (11.1%), hypertension (18.5%), palpable neck swelling (22.2%), limb deformity (22.2%) and fracture (14.8%). The mean serum calcium was 12.2 ± 0.87 mg/dl. Parathyroid adenoma was localized radiologically in all patients and single adenoma was the most common cause in 96.3%. Left inferior parathyroid adenoma was the most common site of involvement in 51.8%.

Conclusions: Hyperparathyroidism at our centre in northeast India has a classic symptomatic presentation with severe bone and renal involvement and younger age at diagnosis, and equal gender distribution.

Keywords: Clinical profile, Hypercalcaemia, Northeast India, Osteitis fibrosa cystica, Parathyroid adenoma, Primary hyperparathyroidism

INTRODUCTION

Primary Hyperparathyroidism (PHPT) is the endocrine disorder caused due to autonomous secretion of parathyroid hormone, with an incidence of 1 in 500 to 1 in 1,000.^{1,2} There are 3 forms of PHPT including overt symptomatic PHPT, asymptomatic PHPT and normocalcaemic variant of PHPT.³ Overt PHPT presents with the "classical features" of skeletal manifestations, nephrolithiasis and neuromuscular complaints; famously described by Fuller Albright as a disease of bones, stones,

moans, and groans.^{3,4} Data from Indian PHPT registry published in 2018 showed that 95% of PHPT were symptomatic disease.⁵ The use of routine biochemical screening since 1970, has led to the emergence of asymptomatic PHPT as the predominant form in the western world.³ There is an increase in incidence of asymptomatic PHPT in India, reported to be around 5-38%.⁶ The normocalcaemic variant of PHPT was first described in 2003 by Silverberg SJ et al in patients being evaluated for osteoporosis, and was described as the symptomatic variant of normocalcaemic PHPT.^{7,8}

Subsequently, asymptomatic variant of normocalcaemic PHPT has also been described when unsuspecting populations are screened with serum calcium and Parathyroid hormone (PTH) levels.⁹ In the United States, the prevalence of normocalcaemic PHPT is 0.86%; while the prevalence of ranges from 0.4% to 11% in other parts of the world.¹⁰⁻¹³

METHODS

This is a retrospective analysis of 27 cases of PHPT who presented to the department Of Endocrinology, Guwahati Medical College and Hospital in last 5 years. PHPT was diagnosed based on presence of elevated serum calcium along with inappropriately raised iPTH (intact Parathyroid hormone). We excluded patients with syndromic association like multiple endocrine neoplasia, secondary and tertiary hyperparathyroidism. The clinical presentation, biochemical parameters, radiological and histopathology findings were reviewed. Fasting calcium, phosphorous, albumin and alkaline phosphatase (ALP) were done on 3 consecutive days. Calcium was corrected for albumin using the formula, Corrected calcium = Total serum calcium + 0.8(4-Serum albumin). Hypercalciuria was confirmed in all patients by 24 hours urine calcium estimation. In patients with hypercalcaemia iPTH level were estimated. Skeletal survey was done in all patients to see for bone involvement. Ultrasonography (USG) Abdomen was done to screen for nephrocalcinosis and nephrolithiasis.

Laboratory Methods: We measured iPTH and 25 Hydroxy (OH) Vitamin D by electrochemiluminescence assay using Roche Cobas e411 analyzer. Serum calcium (reference range 8.4-10.2mg/dl), inorganic phosphate (reference range 2.5-4mg/dl), albumin (reference range 3.5-5mg/dl), ALP (reference range 38-126IU/l), Creatinine (reference range 0.66-1.25mg/dl) and haemoglobin were measured by auto analyzer.

Localization Method: Preoperative localization of adenoma was done in patients with biochemically confirmed hyperparathyroidism with USG Neck and Contrast enhanced CT scan (CECT) of neck and thorax in all cases. 99 Technetium (Tc-99) sestamibi scan was done in 11 patients only as it was not available in our centre during the study period. Postoperatively histopathological examination of the parathyroid adenoma was done in all patients. The patients were monitored for hypocalcaemic signs and symptoms along with serum calcium estimation for at least 7 days postoperatively. Serum iPTH was rechecked 3-7days after surgery. Patient was defined to be cured if iPTH fall by more than 50% and normalization of serum calcium was seen during this postoperative period.

Statistical analysis was performed by the use of SAS 9.3. Data was presented as mean \pm standard deviation. Chi-square test was used for categorical variables and student t test for continuous variables. 'On way ANOVA' was

used for normally distributed data. Statistical significance was set at p value of 0.05.

RESULTS

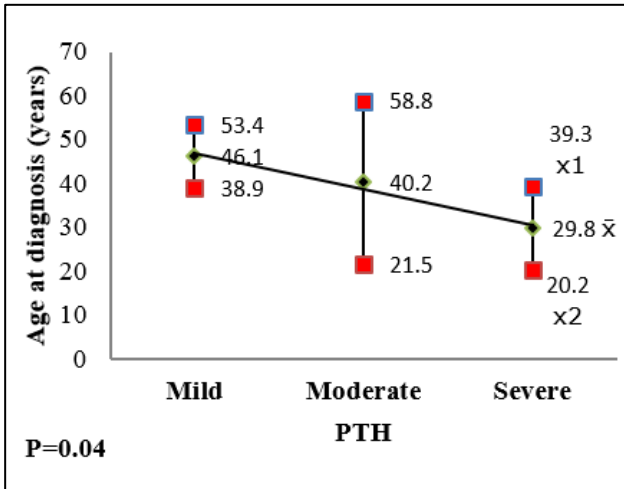
There were 27 consecutive cases who presented to us over a period of 5 years were assessed. The age distribution ranged from 13-72 years (mean 39 ± 16.7). Majority of the subjects (74%) were in the age group of 20-60 years; 18.5% were younger than 20 years and only 7.4% were older than 60years. There were 12 male (44.4%) and 15 female (55.5%) subjects, with male: female ratio being 1:1.25.

Table 1: Baseline characteristics of subjects with primary hyperparathyroidism.

| Clinical presentation | Percent Affected |
|---|----------------------------------|
| Bone disease | 85.1% |
| Bone pain | 59.2% |
| Fracture | 14.8% |
| Neuromuscular manifestations | |
| Proximal myopathy | 48.1% |
| Fatigue | 44.4% |
| Psychiatric manifestations | 7.4% |
| Renal disease | 66.6% |
| Gastrointestinal manifestations | 44.4% |
| Pancreatitis | 3.7% |
| Gall stones | 3.7% |
| Anaemia | 48.1% |
| Hypertension | 18.5% |
| Biochemical parameters | Mean \pm 2SD |
| Serum Calcium (mg/dl) | 12.24 \pm 0.87 |
| Serum Phosphorous (mg/dl) | 2.73 \pm 0.46 |
| Serum Alkaline Phosphatase (U/Lt) | 1098.2 \pm 1378.8 |
| Parathyroid hormone (pg/ml) | 962.5 \pm 683.9 |
| Serum Creatinine (mg/dl) | 1.82 \pm 3.09 |
| 25(OH)Vitamin D (ng/ml) | 19.9 \pm 11.5 |
| Haemoglobin (g/dl) | 9.8 \pm 2.1 |
| Preoperative localization of parathyroid adenoma | Sensitivity |
| Ultrasound neck | 77.7% (21/27) |
| Contrast enhanced CT neck and thorax | 96% (26/27) |

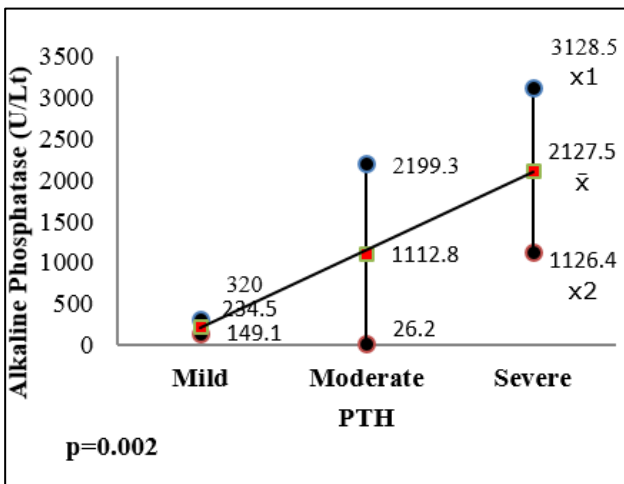
The duration of symptoms at presentation or the lag time of diagnosis, ranged from 2 to 72 months (mean 21.7 ± 20.3). Most common presentation was skeletal manifestation with bone pain seen in 59.2%. Neuromuscular symptoms were next common feature, with proximal myopathy in 48.1% and fatigue in 44.4%. Gastrointestinal symptoms included abdominal pain (44.4%); dyspepsia, constipation, anorexia (11.1%) and nausea (7.4%). Palpable neck swelling was seen in 6(22.2%). Haematuria/graveluria were the presenting complaint in 11.1%, while polyuria was seen in 18.5% of the patients. Deformity of limb in the form of genu

valgum was seen in 7.4% patients, genu varum in 3.7%. Kyphosis was seen in 11.1% and scoliosis in 7.4%. Genu varum with other severe deformity in the form of pectus carinatum, kyphosis, and collapsed vertebrae were seen in 1 patient. No sex preponderance of symptoms was seen (Table 1).



Mild (66-700 pg/ml), Moderate (701-1334 pg/ml) and severe (1335-1968 pg/ml) elevations of iPTH level. \bar{X} = Mean, x1=upper limit of confidence interval (CI), x2=lower limit of CI

Figure 1: One way ANOVA of the age at diagnosis in different preoperative iPTH (intact parathyroid hormone) groups.



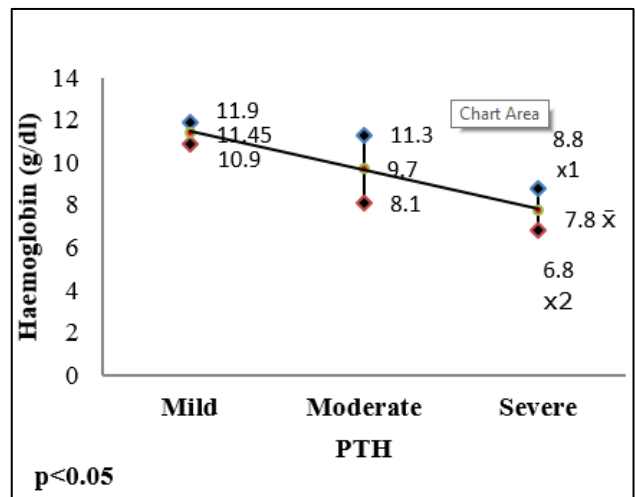
Significantly higher ALP levels were seen in patients with severely elevated iPTH levels. iPTH levels. Mild (66-700 pg/ml), moderate (701-1334 pg/ml) and severe (1335-1968 pg/ml) elevations of iPTH level. \bar{X} = mean, x1=upper limit of confidence interval (CI), x2=lower limit of CI

Figure 2: One way ANOVA of ALP (alkaline phosphatase) levels in different preoperative iPTH groups.

All cases of PHPT had hypercalcaemia, while hypercalcaemic features were seen in 59.2% cases. Hypophosphatemia was seen only in 29.6%. S creatinine was raised in 29.6% above reference range. Serum ALP

was high in 85.2%. Serum 25 Hydroxy (OH) vitamin D level was available in only 15 patients and was deficient (<20 ng/ml) in 50% and in the insufficient (20-30 ng/ml) in 25%. Anaemia (haemoglobin/Hb<10 g/dl) seen in 48.1% cases and was normocytic normochromic in 74%, with the rest showing microcytic hypochromic blood picture.

Intact Parathyroid Hormone (iPTH) was elevated in all patients and >1000 pg/ml in 44.4%. Serum iPTH levels ranged from 66-1969 pg/ml. iPTH levels was divided into 3 tertiles, as mildly (66-700pg/ml), moderately (701-1334pg/ml) and severely elevated (1335-1968) iPTH. 'One way ANOVA' between these groups was conducted, to compare effect of different levels of serum iPTH level on parameters like age at presentation, ALP, Hb levels and postoperative nadir calcium level. There was a significant effect of iPTH levels on these parameters (p <0.05) (Figure 1-4).

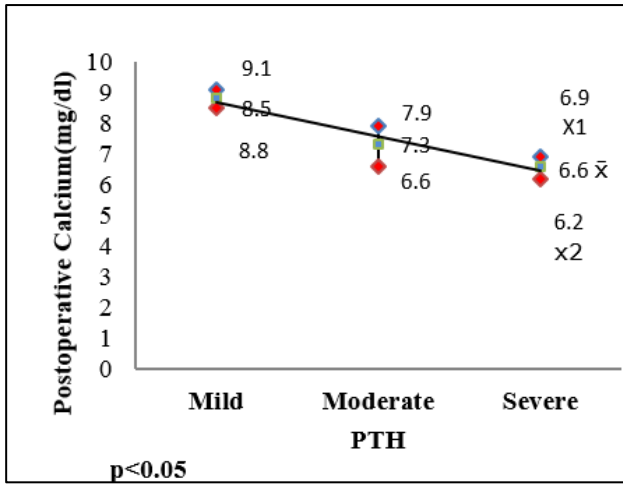


Mild (66-700pg/ml), Moderate (701-1334pg/ml) and Severe (1335-1968pg/ml) elevations of iPTH level. \bar{X} = Mean, x1=upper limit of Confidence interval (CI), x2=lower limit of CI

Figure 3: One way ANOVA of Hb (haemoglobin) levels in different iPTH groups.

Radiological findings included subperiosteal resorption, osteoporosis and osteitis fibrosa cystica (OFC) in 18.5%, pathological fracture in 14.8%, nephrolithiasis in 44.4% and nephrocalcinosis in 22.2%. Renal stones were unilateral in 7.4%, bilateral in 25.9%. Staghorn calculi were seen in 11.1%. Bone mineral density assessed by DEXA in 10 patients showed osteoporosis in 64% and osteopenia in 36%.

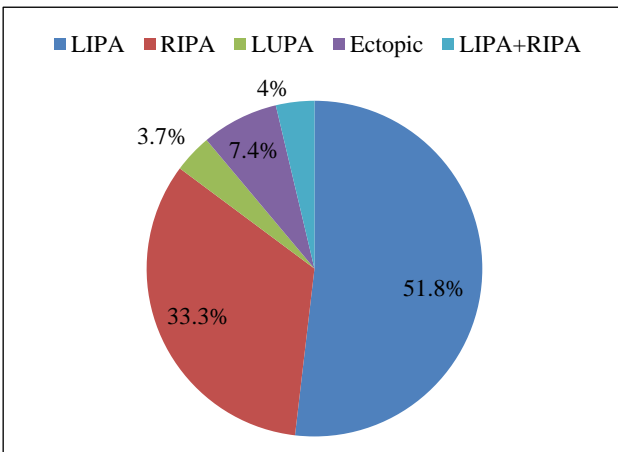
Bone involvement was overall found in 85.1% patients, and both bone and kidney disease were found in 51.8%. Kidney disease alone in the absence of bone involvement was seen in 11.1%. Patients with kidney disease alone had a significant lower iPTH as compared to those with patients with bone involvement (399.5±249.2 vs. 1038.9±698.7, p=0.006).



Mild (66-700 pg/ml), Moderate (701-1334 pg/ml) and Severe (1335-1968 pg/ml) elevations of iPTH level. \bar{X} = Mean, x1=upper limit of Confidence interval (CI), x2=lower limit of CI

Figure 4: One way ANOVA of postoperative calcium levels (hypocalcaemia) in different preoperative iPTH groups.

In preoperative localization, USG was diagnostic in 21/27(77.7%), CECT in 26/27(96%), Tc-99 sestamibi in 11/11 patients. 26 out of 27 patients had solitary parathyroid adenoma, most common site being left side in 55.5%. USG neck showed associated multinodular goitre in 5(18.5%), colloid goitre in 2(7.4%), benign thyroid nodule in 1(3.7%) patient and among them 2 patients had hypothyroidism.



LIPA-Left inferior parathyroid adenoma, RIPA-Right inferior parathyroid adenoma, LUPA-Left Upper parathyroid adenoma

Figure 5: Localization of parathyroid adenoma in subjects with primary hyperparathyroidism.

Postoperatively on histopathology all the patients were found to have adenoma. The mean weight of parathyroid adenoma was 4.2±1.8 grams. No cases of parathyroid carcinoma were seen. Left inferior parathyroid adenoma (LIPA) was most common site of localization in 51.8%. One patient had dual adenoma in left inferior parathyroid

and right inferior parathyroid region. Two (7.4%) of the patients had ectopic parathyroid adenoma, one at the root of neck in left paratracheal region and another in anterior superior mediastinum (Figure 5).

Postoperative hypocalcaemia developed in 59.2% of the patients, by mean duration of 26 hours postoperative (range 18-36hours) and was symptomatic in 44.4%. Hungry bone disease (HBD) developed in 40.7% with persistent hypocalcaemia up to 2 weeks postoperative. Mean duration of i.v calcium gluconate infusion was 4±1.2 days. All patients had transient hypocalcaemia with normal calcium levels off medication at follow up at 3months. Subjects with higher iPTH level had a significant lower nadir postoperative calcium level (p<0.05) (Figure 4).

One of the subjects, with severe HBD had prolonged (>2 weeks) postoperative symptomatic hypocalcaemia. This occurred in spite of correcting vitamin D deficiency in the preoperative period. Patient failed to improve on maximum dose oral calcium (6g/day) and calcitriol (2ug/day) and required intravenous calcium (3-6g/day) for episodes of symptomatic hypocalcaemia even after 2 weeks. Postoperative iPTH after 2 weeks was 42pg/ml; ruling out postoperative hypoparathyroidism. The patient was then started on teriparatide 20ug/day subcutaneously, with which dramatic improvement was seen. Intravenous calcium was stopped and oral calcium was tapered to 2g/day along with calcitriol 1ug/day. Teriparatide was stopped after 4 weeks, following which the subject continued to maintain normocalcaemia with the oral calcium 1.5g/d and calcitriol 1ug/day.

One case of mortality was recorded. A case of diffuse large B cell lymphoma, found to have coexisting primary hyperparathyroidism with palpable neck mass. Patient had high iPTH level, with normal 1, 25 (OH) vitamin D and 25(OH) vitamin D levels. USG neck revealed left inferior parathyroid adenoma. Patient could not be operated due to poor general condition and later succumbed to sepsis and respiratory failure.

DISCUSSION

In this series of PHPT from northeast India we have seen that hyperparathyroidism in this region is severely symptomatic at presentation. Compared to the classic female predominance with female to male ratio of 3:1 described ², in our series we find an almost equal gender distribution with female: male ratio being 1.25:1. Other studies from different parts of India show a higher female preponderance with female to male ratio ranging from 2:1 to 6:1.^{5,6,14-24}

The incidence in hyperparathyroidism is typically described in the sixth decade.³ In our study, 55.5% of the patients were less than 40 years and 18.5% were younger than 20 years (mean 39±16.7). Most of the other studies from India report a similar younger age distribution.¹⁴

^{16,18,19,21} Changes have been seen in the age at presentation, with a shift from fourth to fifth decade in few centres in India. Mallikarjuna VJ et al, reported a higher mean age at incidence of 48.1±15.8 years, while a mean age of 50.8 years was reported by Parmar Get al.^{20,22}

The duration of symptoms at presentation, in our series ranged from 2 to 72 months (Mean 21.7±20.3). The lag time ranging from 1 month to 10 years with a median duration of 2.5 years (37±32 months) has been reported by Indian PHPT registry.⁵ A similar mean time lag of diagnosis was reported by other studies from India.^{14,15,21} A longer mean duration of symptoms of 5.5 years was reported by Maskey et al.¹⁸ The delay in diagnosis is probably due to lack of awareness of symptoms among our population, and absence of screening for serum calcium and routine health check up. This has probably contributed to overt symptomatic disease at presentation in our study, similar to studies in most other parts of India.

Skeletal manifestations (85.1%) were the most common presenting complaint in our study. High incidence of bone involvement seen in our series reflects similar trends in other parts of the country; however prevalence of OFC (18.5%) is less compared to some Indian studies. The prevalence of bone involvement of 47-86.5%, and OFC of 37-58% has been reported in other studies from India.^{4,14,15,17,18,22,24} However, relatively lower rates has been reported by Misgar et al and Mallikarjuna VJ et al with skeletal involvement in 39.7% and 40.7% respectively.^{19,20} Developed nations have seen drastic decrease in the incidence of severe bone and kidney disease, with osteitis fibrosa cystica now seen in fewer than 5%.²

Proximal myopathy was a common (48.1%) of our patients. This classic neuromuscular syndrome of primary hyperparathyroidism has virtually disappeared in the west and is replaced by a less well-defined syndrome characterized by easy fatigue.² Bhansali et al, had a similar high prevalence of weakness and fatigue in 56%, while Muthukrishnan J et al, reported muscle weakness in 47%.^{14,15} However other studies from India have showed lower prevalence of myopathy of 3.7-17%.^{19,20,22}

In the western countries, kidney stones are seen in only 10-25 % of patients with primary hyperthyroidism.²⁵ In contrast, in our series we had higher incidence of renal disease in 66.6%; with nephrolithiasis in 44.4% and nephrocalcinosis in 22.2%. Many other Indian studies have showed similar high incidence, ranging from 40.5% to 70%.^{14,16,18,19} However some studies from India have reported a change in trend with a lower incidence of renal disease similar to western data. Renal disease was reported in 27.7% by Mallikarjuna VJ et al, with nephrolithiasis in 18.5% and nephrocalcinosis in 5.5%.²⁰ Parmar G et al also reported similar lower incidence of renal stones in 23%.²²

All cases of PHPT in our study had hypercalcaemia with corrected total serum calcium >10.5 mg/dl (mean 12.4±1.3mg/dl) while hypercalcaemic features were seen in 59.2% cases only. Conspicuous absence of hypercalcaemic symptom was seen in a series by Harinarayan CV et al.²⁶ This is in contrast to study from north India by Bhansali et al showing hypercalcaemia in 87% and symptoms suggestive of hypercalcaemia in 77%; and another series by Muthukrishnan et al, with hypercalcaemia in 78%.^{14,15} Hypophosphatemia was seen in only 29.6% in our study, whereas higher incidence of 65% and 94% was seen in other series.¹⁶ Another Indian study by Pradeep PV et al, showed normal mean phosphorous level in PHPT patients and presence of hypophosphatemia in only 25% of the patients.¹⁷

High serum ALP was seen in 85.2% and had significant correlation by linear regression with iPTH level (p <0.05). Higher iPTH level was more commonly seen in younger individuals and patients with longer durations of symptoms. Similar high levels were seen in other Indian series.¹⁴⁻²⁴ Among 15 patients in our study mean serum 25(OH) vitamin D level was 19.9±11.5 ng/ml, with deficiency in 50% and insufficiency in 25%. Harinarayan CV et al, reported a mean 25(OH) vitamin D of 8.39±5.09 ug/L (Normal range:14.2-40ug/L). Other Indian series also showed high prevalence of vitamin D deficiency among patients evaluated.¹⁵⁻²³ This is in contrast to series by Bhansali et al where normal levels of vitamin D were seen.¹⁴ Vitamin D deficiency could contribute to the severity of bone disease and could be one reason for higher incidence of bone manifestations in our population.

In our study with anaemia was seen in 48.1% cases, with predominantly normochromic normocytic blood picture (74%). Indian PHPT registry showed higher prevalence of anaemia being reported in other major centres across India ranging from 55.9- 68.8%.⁵ National Family Health survey-4 done between 2015-2016 showed a prevalence of anaemia of 35.7% of the children, 46% in women and 25.4% in men in Assam state.²⁷ However, normocytic normochromic anaemia has also been reported as a complication of PHPT in 5-30%, associated with more advanced bone disease, higher levels of PTH, serum calcium and ALP, with improvement seen after parathyroidectomy.^{28,29} Anaemia in PHPT is multifactorial, and marrow fibrosis due to high levels of iPTH is one of the causes.²⁹ High prevalence of iron deficiency anaemia and overt symptomatic PHPT in our region may both have contributed to a higher prevalence of anaemia seen in our study.

Accurate preoperative localization facilitates directed unilateral explorations and minimally invasive techniques for parathyroidectomy, and reduces operative and recovery-room time, result in significantly fewer postoperative complications.³ In our study, CECT showed good success rates of 96% (26/27), while USG had a lower sensitivity of 77.7% (21/27). Tc Sestamibi Scan

was done in only 11 patients due to non availability at our institute, and is a drawback of our study. Other Indian studies have reported the sensitivity ranging from 65-93% for USG, 63.5 to 93.5% for CECT and 86.9-100% for Tc Sestamibi scan for the localization of adenoma.^{16,17,19,21} USG and CECT are relatively inexpensive and sensitive imaging modality for detection of parathyroid adenoma in resource restricted settings.

In our study, 55.5% of parathyroid adenoma was localized to the left side, with LIPA being the most common site in 51.8%. Bhansali et al, found 70% adenoma on left side, with 56% having LIPA.¹⁴ Marzouki HZ et al, reported that among 147 patients who underwent parathyroidectomy for PHPT, left inferior parathyroid glands were the most common site of adenomas in 41.3%.³⁰ However, Misgar et al, and Parmar et al, reported right inferior gland was involved most often in 57.97% and 35.4% respectively.^{19,22} Gopal V et al, reported 65% of the tumours were from inferior glands with almost equal distribution between right and left side.¹⁶

Postoperative hypocalcaemia developed in 59.2% of the patients in our study. Hypocalcaemia was symptomatic in 44.4% and HBD developed in 40.7%. Bhansali et al, reported 59% developed postoperative hypocalcaemia by day 2 and HBD in 48% subjects.¹⁴ Gopal et al, reported HBD in 30.3% patients.¹⁶ Pradeep et al, reported that out of the 100 PHPT patients, 79 suffered early symptomatic hypocalcaemia and 92 had biochemical hypocalcaemia after parathyroidectomy.¹⁷ Misgar et al, and Muthukrishnan et al, reported lower rate of HBD in 10.12% and 9.8% of the subject respectively.^{15,19} High prevalence of skeletal involvement in our series, could have contributed to the higher incidence of HBS in our study.

CONCLUSION

PHPT in our centre in northeast India has a classic symptomatic presentation with severe bone and renal involvement and younger age at diagnosis, similar to presentation in many parts of India. Lower prevalence of hypercalcaemic symptoms and lower incidence of hypophosphatemia and almost equal gender distribution are unique features. Incorporation of routine serum calcium screening may facilitate early diagnosis in the asymptomatic phase and may prevent the complications seen with classic florid presentation.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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