



Emerging Pattern of Asymptomatic Hyperparathyroidism in South India – a Six-Year Retrospective Study

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Abstract

Introduction: Primary hyperparathyroidism (PHPT) is a common endocrine disease with a variable presentation. There is a recent increase in the number of asymptomatic cases due to the use of multichannel automated analyzers.

Aim: To analyze the changing trend of PHPT patients from South India.

Materials and methods: We collected the data on clinical presentation, biochemistry, radiological features, and operative findings of patients with PHPT treated in our hospital over a period of six years and looked at the differences between symptomatic and asymptomatic PHPT.

Results: Our study included 80 patients. A significant proportion (~41%; n=33) of the patients were asymptomatic. Fifty-seven percent of asymptomatic patients were females. Mean age at presentation of asymptomatic patients was 50.58 (± 14.67) compared to 47.28 (± 14.78) for the symptomatic group, which was not statistically significant ($p=0.34$). The mean levels of serum calcium, phosphorous, 25(OH)D, iPTH, and 24-hour urinary calcium in symptomatic vs. asymptomatic patients were 12.47 (± 2.26) mg/dl vs. 12.27 (± 1.82) mg/dl ($p=0.70$), 2.59 (± 0.74) mg/dl vs. 2.38 (± 0.77) mg/dl ($p=0.27$), 12 (± 1.2) ng/ml vs. 10.85 (± 1) ng/ml ($p=0.78$), 1212.5 pg/ml vs. 678.5 pg/ml ($p=0.31$), and 292.6 mg/day vs. 262 mg/day ($p=0.64$), respectively. When Ca and gland weight were compared with variations in the iPTH levels, there was a significant positive correlation with PTH >600 pg/ml ($p=0.001$) with no between-group differences. The adenoma weight increased by 0.5291 mg for every unit increase in iPTH in the entire cohort, with no between-group differences ($p=0.52$).

Conclusion: Asymptomatic hyperparathyroidism is increasingly being identified in clinical practice and constitutes a significant proportion of primary hyperparathyroidism. Though asymptomatic PHPT is expected to be milder, such a difference in presentation was not obvious in our study.

Keywords

asymptomatic hyperparathyroidism, parathyroid gland weight, trend

INTRODUCTION

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.^[1,2] 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.^[3,4] There is a recent increase in number of asymptomatic cases due to the use of multichannel automated analyzers. We have previously reported that among our cohort of PHPT, 38.9% of patients were asymptomatic and were detected incidentally.^[5]

AIM

We decided to analyze our cohort to look for any differences in the clinical profile and surgical outcomes between symptomatic and asymptomatic PHPT patients who underwent surgery.

MATERIALS AND METHODS

Subjects

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 2016 were included in this study. Patients were diagnosed as having hyperparathyroidism based on the following criteria: 1) Elevated serum calcium level of more than 10.5 mg/dl, and an inappropriately low phosphorous level; 2) Inappropriately high intact parathyroid hormone (iPTH) level.

Measurement of parameters

Serum calcium assay was done using the modified ortho-cresolphthalein complexone method on the Beckman Coulter AU analyzer; the reference range for normal serum calcium in our laboratory is 8.5 to 10.5 mg/dl. Serum phosphate was assessed using modified phosphomolybdate method on the Beckman Coulter AU analyzer; the reference range for normal serum phosphate in our laboratory is 2.5 to 4.5 mg/dl. Intact parathyroid hormone (iPTH) was measured by electrochemiluminescence (ECLIA) sandwich assay (Elecsys system, Roche Diagnostics), with the normal reference range being 15 to 65 pg/ml. 24-hour urinary calcium was measured by a modified ortho-cresolphthalein complexone method; values above 4 mg/kg/24 hours were considered as evidence of hypercalciuria. Urine was collected in a container containing 10-20 ml of 6 N (M) hydrochloric acid (HCl). 25 hydroxy

vitamin D [25(OH)D] was measured by competitive immunoassay (ADVIA Centaur XP system Siemens health-care diagnostics), with a value below 20 ng/ml being considered as evidence of deficiency.

Data collection

Medical records of these patients were retrospectively reviewed for age, sex, previous medical history, presenting symptoms and signs, routine biochemical investigations and histopathological diagnosis, operative and peri-operative findings. Patients were categorized into symptomatic and asymptomatic hyperparathyroidism based on these findings and compared on various variables. Secondary and tertiary hyperparathyroidism cases were excluded. Institutional Ethics Committee clearance was sought for conducting the study.

Statistical analysis

SPSS 21 (Statistical Package for Social Sciences 21, USA) was used for data analysis. The data are expressed as mean \pm standard deviation (SD); 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. A *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Our study identified 80 patients with ages ranging from 16 to 76 years. A significant proportion (~41%; n=33) of the patients were asymptomatic. Subjects in our study showed a female-to-male ratio of 1.43 to 1. Symptomatic group was defined by their clinical presentation.

In the symptomatic group, 15 patients (31.9 %) presented with recurrent renal calculi, 10 patients (14%) presented with musculoskeletal pains, 6 (12%) presented with fractures, 5 (10.6%) presented with pancreatitis, and 3 (6%) presented with neuro-psychiatric symptoms. In addition, 4 patients (8.5%) had a palpable neck nodule, 3 (6%) had evidence of brown tumor, and 3 (6%) had nephrocalcinosis on evaluation. In the symptomatic group, 4 patients required immediate correction for acute severe hypercalcemia. Subjects in the asymptomatic group were identified on evaluation of unrelated sickness such as while evaluating for fever, or preoperative evaluation for unrelated surgery such as cholecystectomy or thyroidectomy. Some patients were detected incidentally on routine health checkups.

We compared the data on symptomatic and asymptomatic groups, and this has been summarized and presented in **Table 1**. In our analysis, 57% of asymptomatic patient were females. Mean age at presentation of asymptomatic patients was 50.58 (± 14.67) compared to 47.28 (± 14.78). The mean serum iPTH levels were almost double in patients who presented with symptomatic PHPT, though this difference was not statistically significant. The levels of calcium, phospho-

Table 1. Comparison of clinical profile in patients with symptomatic and asymptomatic hyperparathyroidism

| Characteristic (Mean) | Symptomatic | Asymptomatic | p-value |
|---------------------------------|----------------------|----------------------|---------|
| Number (n=80) | 47 | 33 | |
| Age in years | 47.28 (\pm 14.78) | 50.58 (\pm 14.67) | 0.34 |
| Sex | Male 19 (40%) | Male 14 (42%) | 0.85 |
| | Female 28 (59%) | Female 19 (57%) | |
| iPTH (baseline) (pg/ml) | 1212.5 | 678.5 | 0.31 |
| Corrected calcium (mg/dl) | 12.47 (\pm 2.26) | 12.27 (\pm 1.82) | 0.70 |
| Phosphate (mg/dl) | 2.59 (\pm 0.74) | 2.38 (\pm 0.77) | 0.27 |
| ALP (IU/l) | 172.5 | 135.5 | 0.245 |
| 25 OH Vitamin D (IU) | 12 | 10.85 | 0.78 |
| 24 hr. urinary calcium (mg/day) | 292.6 | 262 | 0.64 |
| Duration of surgery (mins) | 151 | 150 | 0.55 |
| Gland weight in gms | 4.74 | 2.20 | 0.52 |
| | | | |
| Post-op hypocalcemia | Yes: 3/12 (25%) | Yes: 11/25 (44%) | 0.34 |
| | No: 9/12 (75%) | No: 14/25 (56%) | |

rous, alkaline phosphatase, vitamin D and urinary calcium were very similar between the two groups. Although the duration of surgery did not differ between the two groups, the weight of the excised gland was more than double in the symptomatic group, and this was found to positively correlate with iPTH levels. The adenoma weight increased by 0.5291 mg for every unit increase in iPTH in the entire cohort of patients with PHPT. Both serum calcium and gland weight were found to have significant positive correlation with PTH, at serum iPTH values above 600 pg/ml ($p \leq 0.001$). Contrary to expectation, the incidence of post-op hypocalcemia was higher in the asymptomatic group. Although this was not statistically significant, this observation may allude to the fact that asymptomatic patients were not adequately treated pre-operatively for vitamin D deficiency that seemed equally prevalent in both groups.

DISCUSSION

Primary hyperparathyroidism is a common endocrine condition^[6] with a variable presentation with a spectrum including: a) symptomatic hyperparathyroidism, b) normocalcemic hyperparathyroidism, and c) asymptomatic hyperparathyroidism. There is still a debate amongst clinicians whether to treat asymptomatic PHPT as one end of a spectrum in PHPT or to treat it as a separate entity. The effect on morbidity and mortality including effect on behavioral, renal, gastrointestinal, cardiovascular systems needs to be established, if asymptomatic PHPT is to be treated as a separate entity.^[7-9] In this study, we have attempted to differentiate between the characteristics of symptomatic and asymptomatic cases at the time of detection and see if there are significant differences in their clinical profile.

We found that asymptomatic patients formed a significant portion of our PHPT cohort (41%). However, they

did not differ from the symptomatic group with regards to levels of calcium, phosphorous, alkaline phosphatase, and vitamin D measured in serum; nor was there any noticeable difference in urinary calcium excretion. The asymptomatic patients tended to be older in age, had lower levels of serum iPTH, and exhibited lower weight of the excised gland. Though these differences did not achieve statistical significance, they suggest that we may have detected the disease at an earlier stage and could explain the lack of symptoms attributable to PHPT.

When serum calcium and gland weight were compared with variations in the iPTH levels, there was a significant positive correlation with iPTH > 600 pg/ml irrespective of the group the patient belonged to. The adenoma weight increased by 0.5291 mg for every unit increase in iPTH in the entire cohort. These findings suggest that the degree of hypercalcemia and the size of the gland goes hand in hand with the severity of parathyroid hormone excess, even in patients who were asymptomatic at detection. The incidence of post operative hypocalcemia also did not statistically differ between the two groups, suggesting that significant physiological changes have occurred in the asymptomatic group in a similar fashion to what is seen in classic PHPT. It is noteworthy to mention that asymptomatic PHPT patients are also prone to develop post operative hypocalcemia and should receive appropriate preventive measures and close monitoring during the post-op period.

In comparison to a study by Mithal et al.^[9], done in our country from 2009 to 2012, we found no statistical differences in age at presentation between symptomatic and asymptomatic patients; whereas they found that asymptomatic patients were older. The proportion of asymptomatic PHPT cases were very similar to what we found in our study (38% vs. 41%). When compared to another study by Arya et al.^[10], the proportion of patients diagnosed with asymptomatic PHPT was more in our cohort (10% vs. 41%).

While Arya et al. included patients diagnosed with PHPT from 1995 onwards, our cohort only included patients from 2011 onwards. This difference seen in our study and the one by Mithal et al. probably reflects the changing spectrum of PHPT, with more and more asymptomatic cases being detected as a result of enhanced health screening packages and better access to health care. The adenoma gland weight and iPTH were lower in our findings too, similar to the above-mentioned studies, but these differences were not statistically significant in our cohort. A study by Parfitt et al.^[11] from Michigan reported the clinical course of patients incidentally detected to have asymptomatic PHPT; the mean serum calcium and phosphate levels in their cohort were 11.08 mg/dL and 2.71 mg/dL, respectively. This suggested that incidentally detected asymptomatic patients are likely to have lesser degree of hypercalcemia and less pronounced hypophosphatemia. However, in our cohort of asymptomatic PHPT patients, there was a considerable degree of hypercalcemia (mean calcium – 12.27 mg/dl) and significant hypophosphatemia (mean phosphate – 2.38 mg/dl). We speculate that these differences could be related to the highly prevalent vitamin D deficiency in our cohort along with other environmental and nutritional factors. A recently published analysis of the Indian PHPT registry showed that close to 20% of patients were truly asymptomatic with no renal or skeletal manifestations.^[12] This is in stark contrast with data from the western world, where more than 80% of cases of PHPT are incidentally detected and are asymptomatic.^[13]

Our study does have some limitations. Firstly, it is a retrospective study that has captured available data for analysis. Extensive pre-operative evaluation and assessment may not be possible in all patients as the cost of therapy is completely borne by the patient. Bone mineral density assessment was not done in most of the patients, particularly in those from the lower economic strata. It would have been interesting to see if bone mineral density differed between the two groups; this would have added more value to our study. The relatively small sample size is another limitation, which may have contributed to the lack of statistical significance in the differences observed between the two groups. The strength of our study lies in the fact that this data has been obtained in the last decade and is more likely to be representative of the current trend.

All patients in this cohort were counseled for surgery if calcium levels warranted the same. Those with mild hypercalcemia were given the option of immediate surgery versus watchful observation. Though we have only included those who underwent surgery for this analysis, most patients in our experience opted for surgery as opposed to watchful waiting. This may be influenced by the fact that some patients come from distant and remote areas, which makes frequent follow-up visits very difficult. For many, single visit surgical curative therapy may be a better option when compared to multiple follow up visits with adding costs of investigations. This trend may be different from what is seen in the west, where the incidence of parathy-

roidectomy is maximum in the eighth decade of life^[14], and younger patients opt for watchful waiting more often.

CONCLUSION

Our data obtained from asymptomatic PHPT patients who were incidentally detected reveal that their clinical profile is very similar to those with classical symptomatic PHPT. It is likely that the disease would have evolved in these patients and manifested as classic PHPT if they were left untreated. This leads us to believe that the asymptomatic PHPT patients identified incidentally belong to one end of the spectrum and should be evaluated for renal and skeletal manifestations and should be advised surgical intervention if and when necessary. Awareness among physicians and general practitioners about the need for further evaluation of incidentally picked up asymptomatic hypercalcemia will facilitate prompt referral to a specialist and timely intervention. There is felt need for more detailed and prospective studies comparing the outcomes in cases opting for surgery versus those opting for long-term follow-up.

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Competing Interests

The authors have declared that no competing interests exist.

Author contributions

G.V.: guarantor, literature search, clinical studies, data acquisition, manuscript preparation; V.M.: input of intellectual content, manuscript editing and manuscript review, manuscript preparation; M.V.J.: literature search, clinical studies, data acquisition, manuscript preparation; B.G.: input of intellectual content, manuscript editing and manuscript review; V.A.: input of intellectual content, manuscript editing and manuscript review; G.B.: input of intellectual content, manuscript editing and manuscript review; J.M.: data analysis, statistical analysis

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Новая картина бессимптомного гиперпаратиреоза в Южной Индии – шестилетнее ретроспективное исследование

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Резюме

Введение: Первичный гиперпаратиреоз (ПГПТ) — распространённое эндокринное заболевание с вариабельной клинической картиной. В последнее время наблюдается рост числа бессимптомных случаев из-за использования многоканальных автоматических анализаторов.

Цель: Поэтому мы решили проанализировать тенденцию изменения пациентов с ПГПТ из Южной Индии.

Материалы и методы: Мы собрали данные о клинической картине, биохимии, рентгенологических особенностях и оперативных результатах пациентов с ПГПТ, проходивших лечение в нашей больнице в течение шести лет, и рассмотрели различия между симптоматическим и бессимптомным ПГПТ.

Результаты: В наше исследование было включено 80 пациентов. У значительной части (~41 %; n=33) пациентов симптомов не было. 57 % бессимптомных пациентов были женщинами. Средний возраст на момент обращения бессимптомных пациентов составил 50.58 (± 14.67) по сравнению с 47.28 (± 14.78) для симптоматической группы, что не было статистически значимым ($p=0.34$). Средние уровни сывороточного кальция, фосфора, 25(OH)D, iPTH и 24-часовая экскреция кальция с мочой у пациентов с симптомами и у бессимптомных пациентов составляли 12.47 (± 2.26) mg/dl против 12.27 (± 1.82) mg/dl ($p=0.70$) и 2.59 (± 0.74) mg/dl против 2.38 (± 0.77) ($p=0.27$) mg/dl, 12 (± 1.2) ng/ml против 10.85 (± 1) ng/ml ($p=0.78$) и 1212.5 pg/ml против 678.5 pg/ml ($p=0.31$), 292.6 mg/сут. против 262, статистически не значимо ($p=0.64$) соответственно. Са и вес железы сравнивали с вариациями уровней PTH, наблюдалась значительная положительная корреляция с PTH > 600 pg/ml ($p=0.001$) без различий между группами. Масса аденомы железы увеличилась на 0.5291 mg на единицу увеличения PTH во всей когорте первичного гиперпаратиреоза (без различий между группами) ($p=0.52$).

Заключение: Бессимптомный гиперпаратиреоз всё чаще выявляется в клинической практике и составляет значительную долю первичного гиперпаратиреоза. Хотя ожидается, что бессимптомный ПГПТ будет более лёгким, в нашем исследовании такая разница в проявлениях не была очевидной.

Ключевые слова

бессимптомный гиперпаратиреоз, масса паращитовидной железы, тенденция
