VARIED CLINICAL MANIFESTATIONS OF PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Objective: The objective of this study was to evaluate the clinical manifestations of patients who presented with primary hyperparathyroidism (PHPT).

Methods: This three-year retrospective study was conducted in the Endocrinology department of the Hayatabad Medical Complex, Peshawar. Data of PHPT patients was taken from hospital records between Jan 1, 2020, and Dec 30, 2023. Both male and female patients with PHPT who 18 years of age were or older and had undergone parathyroid surgery were included in the study. Patients with secondary or tertiary hyperparathyroidism, multiple endocrine neoplasia, and those with hypercalcemia from malignancies other than parathyroid carcinoma were excluded.

Results: A total of 55 patients with PHPT were identified, of whom, there were 31 (56.4%) males and 24 (43.6%) females. The mean age of the study participants was 38.8 years. Majority of the patients had musculoskeletal manifestations (40%). This was followed by renal calculi (30.9%). Gastrointestinal manifestations and neurological features were the presenting symptoms in 5 (9.1%) and 1 (1.8%) patient respectively. PHPT was found to be asymptomatic in 2 (3.6%) patients.

Conclusion: This study reported a high frequency of musculoskeltal and renal manifestations in patients with PHPT. Arthralgias, back pain, myalgias, muscle weakness and fractures were common skeletal manifestations, while nephrolithiasis was a common renal manifestation. This reiterates the importance of high clinical suspicion of PHPT in patients presenting with these symptoms.

Keywords: Primary Hyperparathyroidism, Parathyroid hormone, Serum calcium, Serum phosphorus, Serum alkaline phosphatase

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disease which is characterized by an increased secretion of parathyroid hormone (PTH) that leads to hypercalcaemia. Increased secretion of PTH from one or more of the parathyroid glands causes PHPT.[1] The PTH level is typically quite high, however it can occasionally fall into the normal range. When the serum calcium level is raised, detectable or elevated PTH levels are obviously undesirable in both scenarios.[2] The worldwide prevalence of PHPT has been estimated to be in the range of 0.2% to 1.3%.[3] A single parathyroid adenoma is responsible for PHPT in 80% of cases. Whereas 10–15% of cases are caused by four-gland hyperplasia, 5% by multiple adenomas, and less than 1% by parathyroid cancer.[1] The last few years have seen a significant shift in the clinical spectrum of PHPT due to the auto analyser's introduction for routine serum calcium screening, which has led to the detection of this disease at an earlier age and at an asymptomatic stage. Moreover, the use of intact PTH (iPTH) has helped to further limit the differentials of the origin of the disease.[4]

The classical PHPT symptoms are rarely observed in the western population. Instead, the condition is typically identified in otherwise asymptomatic people by routine biochemical testing. On the other hand, PHPT is primarily described as a symptomatic disease with one or more of the traditional and classical clinical symptoms in developing nations and the Asian countries.[5] In this regard, very few studies have been conducted in Pakistan to specifically evaluate the clinical manifestations of PHPT. A study conducted in Karachi, Pakistan revealed that the most common presenting clinical features were musculoskeletal symptoms and renal manifestations.[6] However, additional studies are required in this regard. Thus, the objective of this study was to thoroughly assess the clinical manifestations of this condition. This

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will give the physicians an overview of the current clinical spectrum of the condition which help in early identification of the disease and timely management to improve the overall morbidity and mortality.

MATERIALS AND METHODS

This three-year retrospective study was carried out in the Endocrinology department of the Hayatabad Medical Complex, Peshawar after getting approval from the hospital's ethical committee (approval number 1444). Data of PHPT patients was taken from hospital records between Jan 1, 2020, and Dec 30, 2023. Both male and female patients with PHPT who 18 years of age were or older and had undergone parathyroid surgery were included in the study. To ensure confidentiality, the study patients' identities were kept anonymous.

Patients were diagnosed to have PHPT if they had elevated serum calcium levels or normal serum calcium levels with either elevated or abnormally normal levels of PTH. Patients with hypercalcemia from malignancies other than parathyroid carcinoma were excluded from the study. Likewise, those with high calcium levels because of secondary or tertiary hyperparathyroidism were not included in the study. Also, those suffering from multiple endocrine neoplasia or renal failure were not included.

Data regarding demographic profile of patients, their clinical presentation, symptoms that led to the diagnosis, and laboratory results at the time of presentation, such as serum PTH, calcium, phosphorus, alkaline phosphatase, albumin, renal function tests, and vitamin D levels was gathered. Serum calcium was adjusted for the respective albumin level. Regarding the localization studies prior to surgical management, an Ultrasound using 10–12 hertz high-frequency linear probe by an experienced Radiologist with at least 5 years' experience was performed. 99m-Tc Sestamibi scan was performed by an experienced Nuclear Physician with at least 5 years of experience. The diagnosis of parathyroid adenoma, carcinoma or hyperplasia was made based on histopathology results.

All the clinical characteristics and radiological features were reported as frequency and percentages whereas the biochemical parameters were reported as mean with standard deviation. The statistical analysis was accomplished utilizing SPSS version 20. The difference in the mean levels of serum calcium, phosphorus, alkaline phosphatase and PTH was analysed by using Analysis of variance.

RESULTS

A total of 55 patients with PHPT were identified, of whom there were 31 (56.4%) males and 24 (43.6%) females. Fifty-three (96.45%) were identified to have parathyroid adenoma while 2 (3.6%) were diagnosed to have parathyroid hyperplasia on histopathology report. None of the patients were reported to have parathyroid carcinoma. The mean age of the study participants was 38.8 years. The baseline laboratory parameters are presented in table 1.

Regarding clinical manifestations, 22 (40%) had musculoskeletal manifestations at the time of presentation while 17 (30.9) patients had renal calculi. Gastrointestinal manifestations and neurological features were the presenting symptoms in 5 (9.1%) and 1 (1.8%) patient respectively. PHPT was found to be asymptomatic in 2 (3.6%) patients. The frequency of patients reported to have a combination of musculoskeletal, renal, and gastrointestinal features was 3 (5.5%). These clinical manifestations are presented in table 2.

Out of the various clinical manifestations, the most common feature was renal calculi reported in 17 (30.9%) patients followed by arthralgia along with back pain reported in 5 (9.1%) patients. Pancreatitis was reported in 3 (5.5%) patients while giant cell tumour was found in 2 (3.6%) patients.

Table 1: Baseline Laboratory Parameters of the Study Participants (N=55)

Variable	Mean ± Standard Deviation
Age (years)	38.84 ± 13.03
Calcium (mg/dl)	12.9 ± 1.3
Phosphorus (mg/dl)	2.41 ± .77
Alkaline Phosphatase (mg/dl)	392.9 ± 155.97
Creatinine (mg/dl)	.99 ±.384
24 hour urinary calcium (mg/24 hours)	377.29 ±107.42
Vitamin D (ng/ml)	29.4 ±7.9
Parathyroid hormone (PTH) (pg/ml)	909.97 ± 685.199

Table 2: Clinical Manifestations of patients presenting with Primary Hyperparathyroidism (PHPT)

Clinical Manifestations		Frequency (N=55)	Percentage
Asymptomatic		2	3.6
Musculoskeletal	Arthralgia	2	3.6
	Back pain	3	5.5
	Vertebral fracture	2	3.6
	Arthralgia and Back pain	5	9.1
	Vertebral fracture and Back pain	1	1.8
	Myalgias	3	5.5
	Giant cell tumour	2	3.6
	Muscle weakness	4	7.3
Renal Calculi		17	30.9
Gastrointestinal	Pancreatitis	3	5.5
	Abdominal pain	2	3.6
Depression		1	1.8
Musculoskeletal and Renal		2	3.6
Gastrointestinal and Renal		3	5.5
Gastrointestinal, Renal and Musculoskeletal		3	5.5

DISCUSSION

This study demonstrated that more than 90% of the patients who presented with PHPT presented with the classicals symptoms of the disease. Most of them had either musculoskeletal (40%) or renal (30.9%) manifestations of the disease. This was followed by patients who had gastrointestinal features (9.1%) or a combination of gastrointestinal, renal and musculoskeletal features (5.5%). Only 2 (3.6%) patients were found to be asymptomatic. A study conducted in Pakistan demonstrated that majority of the patients with PHPT presented with musculoskeletal manifestations (58.3%) followed by renal manifestations (27.2%).[6] A study from USA also reported a high frequency of patients with musculoskeletal and renal maniestaomns.[7] Another study from China also reported that majority of the patients who had PHPT presented with bone pains, followed by fracture and urolithiasis.[8] These findings are similar to the findings of our study. Though the study by Pappu et al demonstrated a higher frequency of asymptomatic (15%) PHPT compared to our study 93.6%).[7] This is because of the fact that Pakistan is a developing country and routine screening of calcium is not offered. Therefore, most of the patients present when they are symptomatic.

Approximately one third of the participants presented with some form of musculoskeletal features. Amongst these, muscle weakness (7.3%), myalgias (5.5%), back pain (5.5%), arthralgia (3.6%) and vertebral fracture (3.6%) were common. A similar study from Pakistan reported a high frequency of these musculoskeletal features in patients with PHPT.[6] A study from India also demonstrated that muscle weakness, bone pains and fragility fractures were the predominant manifestations in theses pateints.[9] However a study from Iran has reported a very high frequency (93.5%) of arthralgias, bony deformities, fragility fractures and osteitis fibrosa cystica.[10] Out of the total, 2 (3.6%) patients presented with giant cell tumour. One patient had giant cell tumour in the mandible while the 2nd patient had in the maxillary sinus. Previous studies from Western countries have reported their frequency to be less than 5%.[11,12] A study from USA reported that 2 out of 66 patients with PHPT had giant cell tumours of the jaw.[7] A study from Pakistan also reported a 3.8% frequency of these lesions, emphasizing the fact that giant cell tumours still remains predominant presentation in our region.[6,13] Coexisting vitamin D deficiency may have contributed to the increased frequency and severity of skeletal disease because chronic vitamin D deficiency can increase PTH secretion.

About 30.9% of the study population presented with renal calculi. Nephrolithiasis remains a common clinical manifestation of PHPT, with a prevalence that varies from 5 to 55% based on the severity of PHPT and renal imaging methods.[14,15] Previous studies from India and Pakistan have reported almost similar frequency of nephroloithiasis.[6,16,17]The urine calcium to magnesium ratio, hypomagnesuria,

hypercalciuria, and genetic factors are some of the contributing factors for this this increase occurrence of renal calculi.[18]

Almost 5.5% patients had pancreatitis at presentation. A study from India has reported a high frequency (16%) of pancreatitis in patients with PHPT.[19] Another study has reported 6.2% incidence of pancreatitis in these patients.[20] This is almost like the findings reported in the current study. Patients who had more than one organ involvement had a higher mean serum calcium and a lower serum phosphorus level. These differences in the mean calcium and phosphorus were clinically significant. On the other hand, a higher PTH level was observed in patients with depression and anxiety followed by those who had more than one organ involvement. The difference between the mean PTH levels in these groups was statistically significant. Similar findings have been reported by previous studies as well.[21]

CONCLUSION

This study reported a high frequency of musculoskeltal and renal manifestations in patients with PHPT. Arthralgias, back pain, myalgias, muscle weakness and fractures were common skeletal manifestations, while nephrolithiasis was a common renal manifestation of the condition, this reiterates the importance of high clinical suspicion of PHPT in patients presenting with these symptoms.

LIMITATIONS

Although the study only involved a limited number of patients and was conducted at a single centre, its findings successfully emphasize the morbidity associated with PHPT in our demographic. As such, they may not accurately represent the whole Pakistani population.

The severity of the sickness may have something to do with the fact that a portion of the country's economically disadvantaged people delayed seeking medical attention because of illiteracy, ignorance, and difficulty accessing healthcare facilities.

Author's contribution

SK conceived, designed, participated in data collection, did literature review, performed statistical analysis & drafted the manuscript.

TG participated in analysis, literature review and interpretation of data, and helped in drafting the manuscript.

AHA conceived, designed, did literature review and interpretation of data and critically revised the manuscript.

All authors provided final approval for publication of the manuscript and are responsible for the integrity of the study.

Conflict of Interest

The authors confirm that no conflict of interest exists regarding this research.

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