Primary hyperparathyroidism: retrospective 10-year study of 32 cases

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Abstract

Background Parathyroid glands are endocrine glands that regulate calcium metabolism. Usually four in number, they lie mostly on the posterior aspect of thyroid glands. Primary hyper-parathyroidism (PHPT) refers to a condition wherein they secrete an excess of parathyroid hormone leading to signs and symptoms of hypercalcemia.

Patients and Methods Thirty-two patients of primary hyper-parathyroidism were seen by us in the ten years. Majority of patients were below 40 years of age (88%). Male: female ratio was 1:4. The diagnosis was made incidentally in patients who reported for various signs and symptoms not responding to treatment. High serum calcium pointed to the diagnosis of primary parathyroid hyperplasia. It was confirmed by high level of serum parathyroid hormone and localization of enlarged parathyroid glands by USG / MRI and / or Tc-99 Technetium scan. Of the 32 patients examined, 43 parathyroid glands were excised, five cases had two glands excised; out of these 4 cases underwent parathyroid reimplantation in neck/forearm muscles. One unusual case underwent operation for giant-cell tumor of the head of humerus. This patient presented with excessive vomiting not responding standard medical management in post-operative period.

Results During investigations serum calcium was found to be very high, the diagnosis was confirmed by finding high parathyroid hormone and corroborated by T₉₉ Technetium scan. Parathyroidectomy was done in all cases, of which 59% (18 cases) developed mild to severe tetany due to hypocalcaemia.

Conclusion Primary hyperplasia of thyroid gland is the most important cause of hypercalcemia. Hypercalcemia is found in all cases of PHPT in our series with high parathyroid hormone levels. Majority of our cases have one gland involvement and hypocalcaemia in our series is unusually high following excision of involved gland.

Keywords Primary hyperparathyroid hyperplasia · Hypercalcemia · Intact parathyroid hormone · T₉₉ Technetium/sestamibi scan · Parathyroidectomy · Tetany · Giant cell tumor

Introduction

The history of the discovery of parathyroid glands makes very interesting reading. Parathyroid gland was first found during the performance of autopsy on an Indian one-horned rhinosceros by Sir Richard Owen (England) in 1849–1850. Later, Ivar Viktor Sandstrom (Sweden) found and described the same in various animals and humans in 1880. He called his discovery ‘glandulae parathyroidae’. Eugene Glay found out the endocrine role played by parathyroid glands. In 1909 an American pathologist, William G. MacCallum, recognized that parathyroid deficiency could be mitigated by the injection of calcium salts.

The first parathyroidectomy was performed by Felix Mandle (Vienna) in 1925. Mandle excised parathyroid

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gland from a patient who had died in an accident under local anesthesia and then transplanted the same to a patient suffering from severe von Recklinghausen's disease. This effort at transplantation however failed and the patient died; S.A. Wells reported first successful auto-transplantation of cryo-preserved parathyroid tissue.

Primary hyperparathyroidism is the most important cause of hypercalcemia. It is classified as adenoma, glandular hyperplasia and carcinoma. Secondary hyperplasia is a reactive phenomena mostly due to renal failure. Clinically single gland involvement is adenoma while more than one is hyperplasia. It is difficult to differentiate between the two by light microscopy. Single gland involvement with a normal run of parathyroid tissue is probably an adenoma while multiple glands with total tissue replacement by abnormal cells is hyperplasia. Its cause is not known and sporadic cases seen, but can be inherited as a component of familial endocrinopathies including MEN type 1 and 2A.

Asymptomatic hyperplasia is now the most common pattern in West, though Clark (1989) [1] found only 2 asymptomatic cases out of 103 cases of primary hyperparathyroidism. More and more such cases are reported in western literature, while symptomatic cases are predominant in India, far east, middle east and part of southern hemisphere [2, 3, 4, 5, 6].

Cope(1966) [7] classically described the symptoms related to hyper – parathyroidism as Nephrolithiasis, bone diseases, abdominal pain, pancreatitis psychic moans from fatigue, hypertension and CNS disturbances. Incidence is about 42 per 1,00,000 population and female to male ratio is 3:1 [8, 9, 10].

Patients and methods

This study was conducted in M.G.M. Medical College, M.Y. Hospital, and other Associated Hospitals in Indore in last 10 years. 32 cases were studied. The patients were diagnosed as hyperparathyroidism based on one or more of the following criteria (1) elevated serum calcium level (>10.5 mg/dl) (2) hypercalcaemia (>250 mg/day for female and >300 mg/day for male) and hypophosphatemia (>2.5 mg/ml) (3) inappropriately high intact parathyroid hormone – iPTH (>65 pq/ml) determined by IRMA (4) Characteristics radio graphic features of PHPT (5) histological evidence after parathyroidectomy. Patient with a suggestion of multiendocrine neoplasia and other associated metabolic disorders were excluded from the study. Medical records of these documented PHPT patients were retrospectively renewed for age, sex, previous medical history, presenting symptoms and signs, routine biochemical investigations, radiological findings and histopathological diagnosis. Preoperative localization study included one or more of the following: ultrasonography, CT/MRI Scan and Tc99m

technetium or sestamibi scan, whenever indicated. In two patients incidental parathyroid adenoma detected during thyroid surgery. After surgery study did not reveal any other enlarged parathyroid gland. The results are expressed as mean $\pm$ S.E.

Before parathyroid surgery two patients underwent nephrostomy/PCNL (per cutaneous nephrolithotomy) to relieve uraemia. One unusual case (female, age 26 years) of Giant Cell tumor of head of Humerus (Fig. 1) underwent excision and prosthesis replacement, developed severe vomiting with abdominal pain not responding to usual management. Investigations revealed S-Calcium 14.8, S-phosphorus-3.7, AND Alkaline phosphatase-1963, PTH-730, TC-99m technetium scan showed large parathyroid gland of more than 2 cm (Fig. 3). The same was palpable on clinical examination Excision of this parathyroid gland improved her symptoms restoring normal calcium level.

Results

Twenty six females (77%) and six males were included in this study (Table 1). Mean age was 24.4 (9–61) years. 46.9% patients were below 20 years and 37.5% patients were between 20 and 40 years of age. 14 patients (43.8%) presented with fractures including long bones, ribs or vertebrae, out of which 8

Fig. 1 X-ray – Giant Cell tumor of Head of Humerus – F-30 yrs

patients were bed ridden with multiple fractures and other associate symptoms, 14 patients (43.8%) had bilateral renal stones

Table 1 Age and sex ratio in primary hyperparathyroidism

Age in year	Male	Female	Total
0–10	0	1	1
10–20	1	13	14
21–30	3	4	7
31–40	1	4	5
40–50	1	3	4
Above 50	–	1	1
Total	6	26	32

Table 2 Clinical characteristics of 32 patients with primary hyperparathyroidism

Clinical Manifestation	No. of Patients	%
Bone Pain	25	78.0
Fractures	14	43.8
Renal Stones	14	43.8
Urinary Symptoms	20	62.5
Anorexia/Nausea/Vomiting	11	34.3
Abdominal Pain	20	62.5
Depression	14	43.8
Hypertension	13	40.6

with four patients showing mild to moderate hydronephrosis (Table 2). Twenty patients (62.5%) had Urinary symptoms. One female age 22 years had bilateral cataract, other female 30 years had Giant Cell Tumor of Humerus and one. Three females had unusual associated conduction of Giant Cell tumor of Humerus (Fig. 1), bilateral cataract and bilateral pulmonary calcinosis (Table 4). Two cases had palpable nodule of parathyroid gland confirmed by radio imaging and Tc99 – technetium scan. Table 2 shows the clinical presentation of these 32 patients. Table 3 shows the bio chemical parameters of 30

Table 3 Biochemical parameters of 30 patient with PHPT

Biochemical Parameters	Mean $\pm$ S.D.
Serum Calcium (mg/dl)	12.4 $\pm$ 1.1
Serum Phosphorus (mg/dl)	3.0 $\pm$ 0.8
Serum PTH (ng/L)	632 $\pm$ 386
Serum Alkaline Phosphates (94/L)	780 $\pm$ 314

Table 4 Unusual Associated Pathology with PHPT

- Cataract	1 (22 yr. F)
- Giant Cell Tumor of Head of Humeria	1 (30 yr. F)
- Pulmonary Calcinosis with Healed Tuberculosis	1 (30 yr. F)
- Multi Nodular Thyroid Goitre	2

Fig. 2 U.S.G. – Showing parathyroid gland – enlarged – inferior and posterior aspect of thyroid gland

Fig. 3 Tc99m Technetium Scan showing enlarged parathyroid gland left side

Fig. 4 Patient showing severe tetany following parathyroidectomy

patients, as in two patients PHPT detected incidentally following Thyroid Surgery. Hypercalcemia/Hypophosphatemia was found in all 30 cases. Serum Alkaline phosphatase was raised in 27 of 30 patients (90%). Mean intact parathyroid hormone (iPTH) was raised in all 30 cases.

Radio imaging techniques proved inevitable in localizing PHPT. Ultrasound localized parathyroid nodule in 26 of 30 cases (86.6%) (Fig. 2). MRI Scan 5 out of 6 cases (83.3%), and parathyroid scan either Tc99m sestamibi/technetium in 11 of 11 cases (100%) (Fig. 3).

Forty three parathyroid glands were excised in 32 cases. One case needed second exploration for persistent hypercalcemia. Five cases had two enlarged parathyroid nodes of which one case had one normal looking parathyroid gland. Other 4 cases had excision of their two enlarged parathyroid gland with transplantation of half gland in neck muscles (2 cases) and fore arm muscles (2 cases) successfully. Eighteen patients developed hypocalcaemia post operatively. Four cases were on I.V. calcium for 3 to 4 weeks before accepting oral calcium, of this one needed tracheotomy because of severe tetany (Fig. 4) and respiratory distress. Others were given intravenous calcium for 3 to 7 days followed by oral calcium and Vit D3 preparation.

Discussion

Parathyroid Hormone (PTH) is important in body calcium metabolism along with Vit D. Primary hyperparathyroidism is a common endocrine disorder presenting in 0.1–0.4 percent of population [8, 9, 11]. An increase in prevalence of this disorder was noticed in 1970's following the start of routine screening of serum calcium levels in west [12]. Majority of these patients are asymptomatic and mild symptoms are difficult to correlate with PHPT. A large study of primary hyperthyroidism at Mayo clinic of 10 years follow up failed to answer if surgery is necessary in asymptomatic patients [13]. Symptomatic PHPT is still the predominant

form of the disease in developing countries [4, 5, 6, 14]. Clinical presentation of skeletal manifestation, abdominal pain, renal calculi with urinary symptoms, gastrointestinal and cardiac symptoms, anxiety, depression and sleeplessness are found in various percentage in PHPT. Diagnosis is made in symptomatic patients following investigations as seen in studies by Biyabani, [9] Younes, [13] Norris [16] and Bhansali [10]. Vit Deficiency found in endemic area of some developing countries aggravates the osteitis fibrosa cystica and other related disorder in PHPT [4, 14].

Male : female ratio described in literature is 1:2 or 1:3, [2, 6, 7, 11, 15, 16] in western world, while in our series as also in other series in India and other oriental countries male /female ratio is 1:4 or more [9, 4, 5, 14, 17]. The disease appears to present at a comparatively young age (below 40 years) in India and eastern countries. In our series 88% of patients are below 40 years of age of which 47% are below 20 years, same as in other developing countries [4, 14, 17, 18, 19]. Compared to this, the mean age is reported from developed countries is 55 to 62 years [3, 8, 16, 18] While 22.4 years is the mean age in our series Norris (1947), [16] Dent (1961), [22] Sivula (1985) reported that the majority of patients in their series were above 40 years.

The mean age at presentation is almost two to three decades younger than seen in developed countries. The comparison of age group predominance of this disorder is scientifically not correct. The literature reported from developed countries include asymptomatic patient forming the majority of patient while in developing countries all patients reported are symptomatic involving younger age group. The younger age of presentation may be due to prevalence of Vit D deficiency or related to genetic profile of the population [5, 14, 18, 19].

Musculo-skeletal manifestations in PHPT are the most common presenting symptoms in most of the literature [17, 6, 20, 21, 4, 5]. In our series 70% of patients presented with these symptoms with 41%, having pathological fractures. Classic osteitis fibrosa cystica (OFC) in PHPT used to be a common features in literature in west before 1960 [1, 2] now seen in very few cases. In Indian series osteoporosis and occasional lytic lesions are commonly seen in large numbers but OFC is uncommon. Mishra (2001) [6] still feels a large percentage of patients develop osteitis fibrosa cystica. Bhansali [10] found OFC in 58% of patients. Similarly high frequency of bony involvement is reported from other eastern countries [7–9 17].

Hypercalcemia is caused by hypersecretion of parathyroid hormone. The same is observed in our study and various other series [3, 22]. One previous study in India by Hari Narayan (1995) [18] reported normocalcemia in 50% of cases in Vit D deficiency. Hypercalciurea also is common feature of hypercalcemia leading to different urinary symptoms in 50–60 % cases with or without renal calculus. In this series 62% patients had urinary symptoms of frequency, dysuria, hematuria while 43.8% had renal calculus. In

other reported series in India, renal calculus was present in 50–55% of cases [3–5, 17, 18]. The recent literature shows less than 10% of PHPT cases had renal calculus [11, 12, 15, 23]. Bhansali [10] reported 70% patients were presented with renal calculus in PHPT.

Abdominal pain, dyspepsia, nausea, substernal heaviness and retrosternal burning pain due to GERD are common symptoms found in more than 50% of PHPT [8, 11, 12, 16]. Such symptoms are less common in Indian patients and so also in developing countries [2, 6, 14, 19]. We did have 34.3% patients having such symptoms. Lack of energy and concentration, anxiety, irritability, sleeplessness, nervousness and depression due to high calcium level affecting neurogenic cells were found in large number of patients from 50 to 75%; in our series 43.8% patients had such symptoms.

High blood pressure is another common symptoms found in large numbers of patients; other cardiac problems like palpitations and arrhythmias are not uncommon in western literature (5–40%) [8, 10, 12, 16]; 40.6% of our patients had hypertension.

Preoperative localization by ultrasonography, CT-scan, MRI-scan and radio nucleotide imaging with Tc99m, thallium technetium and sestamibi are non invasive procedures available with variable sensitivity [26]. Tc99m sestamibi is sensitive in 90–95% cases. In our series, USG (22 out of 31), MRI (14 out of 16) and Tc-99m technetium scan (12 out of 12) showed more sensitivity in localizing PHPT [24, 25, 26].

Thirty two cases underwent operation with excision of 43 parathyroid glands. One case needed re-exploration for persistent hypercalcemia. 5 cases had two enlarged parathyroid glands; in 4 cases excision with transplantation was needed. Different series show different numbers of single or multiple parathyroid glands involvement with PTHP. Post operative hypocalcaemia was found in 18 cases (59.4%). They needed I.V. Calcium for 7 to 21 day followed by oral calcium, unlike studies in west [10, 13, 19].

Two cases operated for multinodular goitre were found to have one parathyroid gland enlarged and were excised. These were reported as parathyroid adenoma and had not been diagnosed preoperatively. Such incidental parathyroid hyperplasia is not uncommon during thyroid surgery. One unusual case of Giant Cell Tumour in a young female with multiple fractures missed the diagnosis of PHPT because routine serum calcium was not done.

Conclusion

PHPT is the most important cause of hypercalcemia. Symptomatic PHPT are reported, but since last two decades many series from developed countries show an increase in the diagnosis of PHPT in asymptomatic patients. These do not need surgical management. In developing countries

like India, South East Asia and Middle East symptomatic patients constitute the majority of PHPT patients.

In Western literature most common age at presentation is 60–65, female:male ratio is 3:1, while in this series and other India, South East Asia, Middle East the most common age group is 20–40 years, female:male ratio is 4:1. Hypercalcemia and high parathyroid hormone level was found in all cases of PHPT in our series. Hypercalciuria was seen in all cases with or without renal stones. In literature however, it is high in PHPT patients with renal calculus but normal in a high percentage of patients who don't have renal calculus. Serum alkaline phosphatase was high in all our cases. Radiological imaging with USG, CT, MRI and Tc99m technetium or sestamibi scan localizes the parathyroid hyperplasia/adenoma in almost all cases. Majority of our cases had one gland involvement. Symptoms following surgery subside gradually with clinical improvement. Hypocalcaemia in our series following excision of involved parathyroid gland was unusually high. Persistent hypercalcemia despite surgery needs further investigation and localization of undetected parathyroid hyperplasia. If two or more glands are excised, it is advisable to transplant atleast half of one gland in the neck or forearm muscle to prevent hypocalcaemia.

Routine serum calcium surveys in Asian countries and Middle East may help in recognizing many asymptomatic cases as well as the symptomatic ones.

References

- Clark OH, Duh Qy (1989) Primary Hyperthyroidism. A Surgical Perspectives Endocrinal Metal. *Cli North Am* 18:701–714
- Cope O (1996) The study of hyperparathyroidism at the Massachusetts General Hospital. *N Engl J Med* 21(1):174–182
- Sivula A, Ronni Sivula H (1987) Natural history of treated primary hyperparathyroidism. *SURA Clin North Am* 67: 329–341
- Silver Berg SJ, Bilezikian JP (2004) Asymptomatic primary hyperparathyroidism a Medical Prespective. *Surg Cli North Am* 84:787–801
- Boonen S, Vanderschueren D, Pelemans, Bouillon R (2004) Primary hyperparathyroidism diagnosis and Management in the older individuals *European Journal of Endocrinology* 151:297–304
- Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP (1999) A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 21:341(17):1249–1255
- Health H III, Hodgson SF, Kennedy MA (1980) Primary hyperparathyroidism. Incidence morbidity and potential economic impact in a community. *M Engl J Med* 302:189–193
- Scholz DA, Purnell DC (1981) Asymptomatic primary hyperparathyroidism. 10 years prospective study. *Mayo Clin Proc* 56:473–478
- Biyabani SR, Talati J (1999) Bone and renal stone disease in patients operated for primary hyperparathyroidism in Pakistan: is the pattern of disease different from the west? *J Pak Med Assoc* 194–198
- Bhansali Anil et al (2005) Primary hyperparathyroidism in North India : a description of 52 cases. *Ann Saudi Med* 25(1):29–35
- Rao DS, Agarwal G, Talpos GB, Phillips ER, Bandeira F, Mishra SK, Mithal A (2002) Role of Vitamin D and Calcium nutrition in disease expression and parathyroid tumor growth in primary hyperparathyroidism: a global perspective. *J Bone Miner Res* 17 Suppl 2:N 75–80
- Mishra SK, Agarwal G, Kar DK, Gupta SK, Mithal A, Rastad J (2001) Unique Clinical Characteristics of Primary hyperparathyroidism in India. *Br J Surg* 88:708–714
- Younes NA, Al-Trawneh IS, Albesoul NM, Hamdan BR, Sroujeh AS (2003) Clinical spectrum of primary hyperparathyroidism. *Saudi Med J* 24(2):179–183
- Harinarayan CV, Gupta N, Kochupillai N (1995) Vitamin D Status in Primary hyperparathyroidism in India. *Clin Endocrinol (Oxf)*. 43:351–358
- Sivula A, Ronni Sivula H (1985) Observation on 334 patients operated on for primary hyperparathyroidism. *Ann. Chir Gynaecol* 74:66–73
- Norris EH (1947) The Parathyroid adenoma – a study of 322 cases. *Surg Gyne Obst* 84:1–41
- Kapur MM, Agarwal MS, Gupta A, Misra MC, Ahuja MMS (1985) Clinical and Biochemical Features of Primary hyperparathyroidism. *Indian J Med Res* 81:607–612
- Parfitt AM, Rao DS, Kleerekoper M (1991) Asymptomatic primary hyperparathyroidism discovered by multichannel biochemical screening : Clinical course and consideration bearing on the need for surgical intervention. *J Bone Miner Res* 6 Suppl 2:S97–S101; discussion S121–S124
- Ingemansson SG, Hugosson CH, Woodhouse NJ (1988) Vitamin D deficiency and hyperparathyroidism with severe bone disease. *World J Surg* 12: 517–521
- Mirsaeed Ghazi AA, Bostani I, Nasri H, Amiri Z, Rahimi F, Nafarabadi T. Arbab P (2000) (Primary hyperparathyroidism: a report on 30 cases). *Journal of the Shaheed Beheshti University of Medical Sciences and Health Services* 23(4):301–308
- Adami S. Marcocci C, Gatti D (2002) Epidemiology of primary hyperparathyroidism in Europe. *J Bone Miner Res* 17 Suppl 2:N18–N23
- Brasier AR, Nussbaum SR (1988) Hungry bone syndrome : clinical and biochemical predictors of its occurrence after parathyroid surgery. *AM J Med* 84(4):654–660
- Dent CE, Hartland BV, Hicks J, Sykes ED (1961) Calcium intake in primary hyperparathyroidism. *Lancet* 12:336–338
- Drueke TB (1998) Primary and Secondary Uraemic hyperparathyroidism: from initial clinical observations to recent findings. *Nephrol Dial Transplant* 13(6):1384–1387
- Chen CC, Skarulis MC, Fraker DL, Alexander HR, Marx SJ, Spiegel AM (1995) Technetium-99m-sesta mibi imaging before reoperation for primary hyperparathyroidism. *J Nucl Med* 36:2186–2191
- Neumann DR, Esselstyn CB, Macintyre W.J. Go RT, Obuchowski NA, Chen EQ, Licata AA (1996) Comparison of FDG-PET and sestamibi-SPECT in primary hyperparathyroidism. *J Nucl Med* 37:1809–1815
- Mitchell BK, Merrell RC, Kinder BK (1995) Localization Studies in Patients with hyperparathyroidism. *Surg Clin North Am* 75:483–498