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Spectrum of Parathyroid Surgery in Primary Hyperparathyroidism in Eastern India, Kolkata

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ABSTRACT
Parathyroid hormone is the main hormone for calcium homeostasis in our body. It is the third most common endocrine disorder after diabetes mellitus and thyroid disease. This study also aimed to find out the sensitivity and specificity of pre-operative investigations and the etiologic diagnosis of primary hyperparathyroidism and types of surgical exploration, immediate post-operative complications in Eastern India. In this hospital based study out of 34 patients 22 patients were under retrospective study and 12 were under prospective study. All the patients were clinically and biochemically diagnosed cases of hyperparathyroidism irrespective of age and sex, who presented to the both surgery or endocrine OPD, IPGME and R/SSKM Hospital, Kolkata, West Bengal, India between January, 2008 to December, 2012 were included in this research work. Most of the patients were symptomatic 18(52.9%) and all (34 patients) had increased pre-operative intact parathormone (iPTH-1) with hypercalcemia, 28(82.4%) patients had pre-operative hypophosphatemia. Out of 34 patients 33 had parathyroid adenoma underwent focused unilateral adenoma excision and 1patient had parathyroid hyperplasia underwent bilateral subtotal excision. In our research study we found hypercalcemia with increased pre-operative intact serum parathormone level is the most common feature in primary hyperparathyroidism and most patients had parathyroid adenoma in Eastern India.

INTRODUCTION

Parathyroid hormone is the chief hormone that regulates calcium homeostasis in human body. Primary hyperparathyroidism (PHPT) occurs from inappropriate overproduction of parathyroid hormone from one or many parathyroid gland (S) and presents with hypercalcemia. It is the third most common endocrine disorder that affects 0.3% of general population of which 1-3% are postmenopausal women and has a total population incidence of 21.6 cases per 100,000 person years[1-3]. PHPT usually occurs as a consequence of sporadic parathyroid adenomas or carcinomas but it has also been associated with multiple endocrine neoplasias and in rare genetic syndromes and metabolic diseases[4]. It has been seen that in many parts of the world, PHPT has evolved from a disease with severe symptoms of hypercalcemia, i.e. overt bone disease, neuromuscular dysfunction and renal stones, abdominal groans towards a disorder in many patients having described as latent or subclinical with few or no symptoms[5,6]. However, the presentation of the disease is demographically different and it has been proved in developing countries where PHPT patient's presents with more advanced symptomology, and that may be because of delayed diagnosis[7]. From a full exploration of the neck, along with mandatory identification of all glands to minimal invasive surgery, the surgical procedure of parathyroidectomy has been shifted along with few complications and tolerable by most patients[8,9]. It is due to new techniques in the field of radiology enabling accurate pre-operative localizations diagnostics procedures. The aim of our study was to find out the clinical profile of primary hyperparathyroidism of patients and to identify the subset of patients taken for surgery. This study also aimed to find out the sensitivity and specificity of pre-operative investigations and the etiologic diagnosis of primary hyperparathyroidism and types of surgical exploration, immediate post-operative complications.

MATERIALS AND METHODS

In our research study, Out of 34 patients 22 patients were under retrospective study and 12 were under prospective study. All the patients were clinically and biochemically diagnosed cases of hyperparathyroidism irrespective of age and sex, who presented to the both surgery or endocrine OPD, IPGME and R/SSKM Hospital, Kolkata, West Bengal, India between January, 2008 to December, 2012 were included in this research work. Patients with secondary and tertiary hyperparathyroidism, MEN syndrome were excluded in our research work. We measured BMI, pre-operative serum calcium, post-operative serum calcium, intact parathormone (iPTH)-1(pre-operative), intra-operative iPTH-2 (10mins after excision of gland), iPTH-3(after third post-operative day), iPTH-4 (after six months of operation), serum phosphate (preoperative), urinary calcium (pre-operative), uric acid (pre-operative), alkaline phosphatase (pre-operative) in standard methods. We also did radiological investigation like Ultrasonography (USG) of neck, CT-Scan of neck; Technetium (99mTc) sestamibi scan and X-ray of long bones of body, fingers. The patients who were symptomatic either have bony symptoms like pain in long bones, pathological fractures or renal symptoms like loin pain, kidney stone. Computer generated random numbers are used for randomization. Statistical Analysis was performed with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Descriptive statistical analysis was performed to calculate the means with corresponding standard errors (s.e.). The p-value of ≤ 0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

(Table-1) shows distribution of patients according to Clinical, Biochemical and Radiological parameters. In table-1the mean age (mean±sd) of the patients was 38.11±4.24 years with range 30-46 years and the median age was 37 years. Test of proportion showed that the number of the patients in the age group 35-44 years (73.6%) were significantly higher than other age group (Z=3.39., p<0.01). All the 34 (100%) patients were from middle socio-economic background. Test of proportion showed that the proportion of females (70.6%) were significantly higher than males (Z=3.40., p<0.001). The mean BMI (mean±s.d) of the patients was 22.41±1.63 Kg/m2 with range 19-25 Kg/m2 and the median BMI was 22.50 Kg/m2. Test of proportion showed that the proportion of patients with BMI ranged between 20-25Kg/m2 (94.1%) were significantly higher (Z=7.27., p<0.001). The mean level of Serum calcium (mean±s.d) of the patients was 13.72±1.45 mg/dl with range 11.5-18.5mg/dl and the median was 13.5mg/dl. Test of proportion showed that the proportion of patients with level of serum Calcium 11.5-15.4 (87.9%) was significantly higher (Z-5.52., p<0.001). The mean iPTH-1 (mean±s.d) of the patients was 600.35±427.76pg/mL with range 235-1822.0 pg/mL and the median was 460.5pg/mL. Test of proportion showed that the proportion of patients with of iPTH-1(<1000), (82.3%) was significantly higher (Z-5.33, p<0.001). iPTH-2 measurement shows 19 (55.9%) had in the range of 100-200 pg/mL and was statistically significant (p<0.001). iPTH-3 measurement shows 19(55.9%) had in the range of $\geq$10 pg/mL and was statistically significant (p<0.001). All the patients had normal iPTH-4 (10-65 pg/mL) level at 6 months follow up period. Test of proportion showed that the proportion of pt having adenoma was significantly higher than hyperplasia (p<0.0001).Test of proportion showed that there was no significant difference in the proportion of pt having asymptomatic and

Table-1: Distribution of Patients According to Clinical, Biochemical and Radiological Parameters

			No of patients	Percentage (%)	p-value
Age(years)	30-34		6	17.6	<0.01*
	35-39		14	41.2	
	40-44		11	32.4	
	45-49		3	8.8	
Gender	Female		24	70.6	<0.001*
	Male		10	29.4	
BMI(Kg/m2)	<20		2	5.9	<0.001*
	20-22		15	44.1	
	23-25		17	50	
Serum Calcium (normal- 8.0-10.5 mg/dl)	11.5-13.4		15	44.1	<0.001*
	13.5-15.4		14	41.2	
	15.5-17.5		4	11.8	
	>17.5		1	2.9	
Intact parathormone -1(normal-10-65 pg/mL), (Pre-operative)	<500		18	53	<0.001*
	501-1000		10	29.4	
	-1500		3	8.8	
	>1500		3	8.8	
Intact parathormone-2 (normal-10-65 pg/mL pg/dl), (10 mins after excision)	<100		4	11.8	<0.001*
	100-200		19	55.8	
	≥200		11	32.4	
Intact parathormone-3 (normal-10-65 pg/mL pg/dl), (after 3rd day of operation)	<10		15	44.1	<0.001*
	≥10		19	55.9	
Type of Patients (Based on intra operative findings)	Adenoma		33	97.1	<0.0001*
	Hyperplasia		1	2.9	
Symptoms	Asymptomatic		16	47.1	>0.05
	Symptomatic	Bony	8	23.5	
		Renal	10	29.4	
Serum Phosphate (normal- 3.5-5.5 mg/dl)	Normal		6	17.6	<0.001*
	Low		28	82.4	
Clinical Diagnosis	Palpable		8	23.5	<0.05*
	Non palpable		16	76.5	
USG	Positive		28	82.4	<0.001*
	Negative		6	17.6	
CT-Scan	Positive		27	79.4	<0.001*
	Negative		7	20.6	
Type of Surgery	Bilateral		1	2.9	<0.001*
	Unilateral Focused Exploration		33	97.1	
Type of Excision	Adenoma		33	97.1	<0.001*
	Subtotal		1	2.9	
Post-Operative Symptoms	Asymptomatic		17	50	>0.05
	Hungry Bone		17	50	

symptomatic (p>0.05). Test of proportion showed 28 (82.4%) patients having low serum phosphate was significantly higher than normal (p<0.001) in pre-operative patients. USG significantly detected higher number of patients correctly (p<0.001) and CT scan of neck was positive for 79.4% pt among which 2 were mediastinal location (p<0.001). Preoperative Technetium (99mTc) sestamibi scan showed 100% sensitive in our patients. Table showed 33(97.1%) patients were undergone unilateral focused exploration which was statistically significant (p<0.001).Proportion of non palpable patients were significantly higher (p<0.05). Adenoma excision done by unilateral focused exploration in 33(97.1%) of patients and bilateral exploration on one patients where intra operative hyperplasia suspected. Distribution shows 50% of patients had post-operative hungry bone syndrome and there was no significant diff in post-operative asymptomatic and hungry bone syndrome patients (p>0.05). In histopathological report of all 34 patients were consistent with parathyroid tissue without any lymphovascular invasion and high mitotic index. Technetium (^{99m}Tc) sestamibi scan showing left parathyroid adenoma in (fig. 1). (Fig. 2) describes ectopic mediastinal parathyroid adenoma. (Fig. 3) shows subperiosteal resorption of phalanx. (Fig. 4) shows Patient with hyperparathyroidism jaw tumor syndrome. (Fig. 5) shows focused parathyroid adenoma excision.

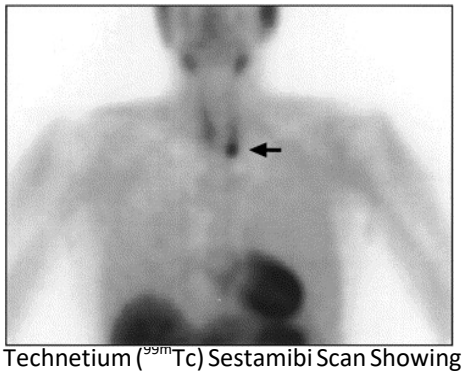

Fig. 1: Technetium (^{99m}Tc) Sestamibi Scan Showing Left Parathyroid Adenoma

Fig. 2: Ectopic Mediastinal Parathyroid Adenoma

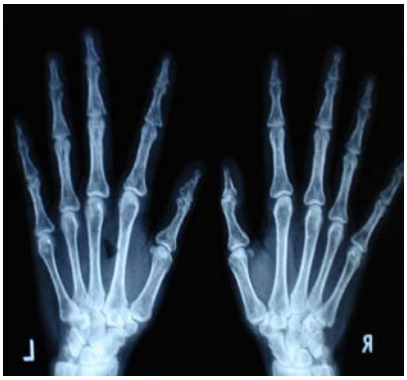

Fig.3, Subperiosteal Resorption of Phalanx

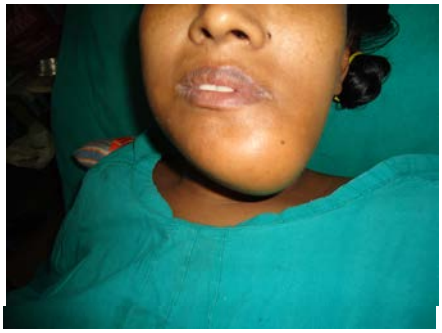

Fig. 4: Patient with Hyperparathyroidism Jaw Tumor Syndrome

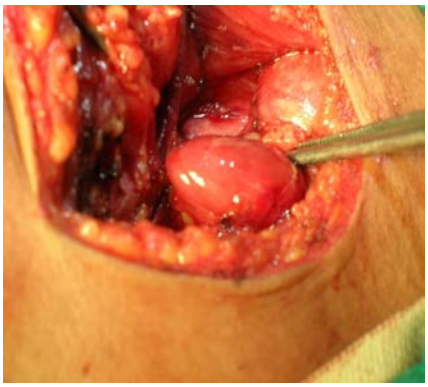

Fig. 5: Focused Parathyroid Adenoma Excision

PHPT is an endocrine disease and is associated with disturbance the hormonal functioning of the parathyroid glands that could lead to production of excessive serum calcium levels. Embryo genesis shows, the parathyroid glands have a close relation to both the thyroid and thymus with same origin[10]. There are three different pathological lesions cosisting of PHPT. Adenoma-benign neoplasm, usually affecting a single gland and the most common lesion found in up to 85% of all cases of PHPT. Hyperplasia-associated with an increase in hormonal active cells in all glands (multi glandular), in the absence of known stimulus for PTH hyper secretion. It consists of 15% of all PHPT cases and may be associated with genetic disturbance in inherited multiple endocrine neoplasia. Carcinoma-a rare condition representing <1% of all PHPT cases. PHPT is found in both genders, among all age-groups, rarely in children[11]. With age the incidence increases and women are more prone to suffer than men. The ratio at older age between female and male is 3:1[5,12-14]. Before 1970s, PHPT was a disease of recurrent kidney stones, osteitis fibrosa cystica, neuromuscular dysfunction characterized by type II muscle cell atrophy[15,16] and symptomatic hypercalcemia but it has now been detected with incidental finding of hypercalcemia with majoty having mild symptoms or asymptomatic[16]. Among 15%-20% of newly diagnosed patients with primary hyperparathyroidism, kidney stone was more common as classical sign[17]. PHPT affects compact bone more than trabecular bone with cortices of long bones are more sensitive leading to subperiosteal resorption of bone (as periosteal elevation on plain radiography)[18],. Fatigue, weakness in muscle, mild cognitive disturbances, hypertension, left ventricular hypertrophy, calcification of heart valves and cardiovascular mortality are less specific features of PHPT[19,20]. In our study Most of the patients were in the middle age group with female preponderancy. Hypercalcemia with increased preoperative intact serum parathormone level is the most common feature Most of the patient shows serum hypophosphatemia. Majority was symptomatic either having bony symptoms like bony pain, pathological fractures or renal stones, renal colic. In most of cases the adenoma was near left lower pole of thyroid. All patients had pre-operative increase urinary calcium excretion (›400mg/24 hrs). The Technetium (^{99m}Tc) sestamibi scan single photon emission CT identifying up to 89% of single parathyroid and adenomas is the most useful modality of investigation today[21-24]. Technetium-labelled sestamibi 99 (mTcMIBI) is taken up by parathyroid and thyroid tissue. Prolonged and enhanced uptake is seen in adenomatous and hyper plastic parathyroid. Ultrasound is the second most useful modality and when it is used with Technetium (^{99m}Tc) sestamibi scan preoperatively can increase detection rates of adenoma. Plain computed tomography and magnetic resonance imaging found as less useful except in in case of ectopic production[25]. The new standard has been accepted by most surgeons is pre-operative radiologic localization of adenomas for a focused parathyroidectomy using unilateral neck exploration and added measurement of intraoperative PTH[26-28]. In our study Technetium (^{99m}Tc) sestamibi scan showed 100% sensitivity in detecting adenoma. Unilateral focused neck exploration followed by adenoma excision done in 97.1% patients. 2(5.9%) patient had ectopic mediastinal parathyroid adenoma detected by CT scan. Cases of Familial hyperparathyroidism associated with MEN1 and MEN2A and familial isolated hyperparathyroidism are also treated surgically[29-31]. MEN1-associated hyper parathyroidism patients present earlier age than sporadic patients but with similar symptoms. We had 1 patient with browns tumor and one had hyperparathyroidism-jaw tumor syndrome which is an Autosomal Dominent familial

hyperparathyroidism. Parathyroidectomy is usually associated with persistent hyparathyroidism if insufficient disease-causing tissue is removed recurrent laryngeal nerve injury, hematoma, infection, pneumonia, transient or permanent postoperative hypocalcemia and seizures due to hypocalcemia and hypomagnesemia[32-35]. We found hungry bone syndrome in 50% of patients on 3-4 post operative day without any other complications and managed with parenteral calcium and Vitamin-D supplementation. We conclude that hypercalcemia with increased pre-operative intact serum parathormone level is the most common feature in primary hyperparathyroidism. We also conclude that most of the patients had serum hypophosphatemia and majority was symptomatic either having bony symptoms or renal symptoms in our clinical practice.

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