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CLINICAL AND METABOLIC CHARACTERISTICS OF PRIMARY HYPERPARATHYROIDISM IN DIFFERENT AGE GROUPS- A TERTIARY CENTRE EXPERIENCE

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ABSTRACT **Background and Objectives-** Symptomatic Primary Hyperparathyroidism (PHPT) is common in India in comparison to the western population. But there is very little data on the influence of age on the presentation of PHPT. In the present study we aimed to analyse the clinical and metabolic profile among different age groups of symptomatic primary hyperparathyroidism. Methods: This retrospective analysis was done in PHPT patients who attended Department of Endocrinology, Gauhati Medical college and Hospital. Thirty-one PHPT subjects who presented to us over a period of last five years were divided into three different age groups i.e, children and adolescents <18yrs, adults ≥18-50 years, and older group >50years. All major clinical, metabolic and imaging parameters were compared among these groups. Appropriate statistical methods were used to compare different variables. **Results:** The age distribution ranged from 13 to 72 years with mean age of 38.6±16.3years and with equal female to male ratio. Bony deformity (Rickets) as initial manifestation was seen in three adolescents and bone pain was common in adolescents(p=0.05). Prevalence of renal stones were higher in adult group(p=0.002), gastrointestinal manifestations were higher in older group (p=0.02). There was no significant difference in fracture rate(P=0.17), brown tumours(P=0.56) and other symptoms among different age groups. Alkaline phosphatase(p=0.006) and iPTH(p=0.01) were significantly higher in adolescent group. There was no significant difference in serum calcium, phosphate, 25(OH)Vitamin-D3 and haemoglobin levels among different age groups. **Interpretation & Conclusion:** Age has substantial influence on PHPT presentation. Bone pain and deformity was common in adolescents, while renal stones and gastrointestinal manifestations were common in middle aged and elderly group respectively.

KEYWORDS : Age, Bone pain, Bone deformity, Primary hyperparathyroidism, Parathyroid adenoma, Symptomatic hyperparathyroidism.

Introduction:

Primary Hyperparathyroidism (PHPT) is an 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 three 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]. Multiple authors have looked at how race, gender, extremes of age, and obesity can influence disease presentation and severity in PHPT [7-11]. However, little data exist stratifying patient age at presentation to evaluate presenting characteristics, management, and outcomes[12]. It is unclear if the disease presentation by way of symptomatology and biochemical indices actually differs based on age. The present study was undertaken to analyse the clinical and metabolic profile among different age groups of symptomatic PHPT presenting to a tertiary care centre.

Materials and Methods:

This observational study was done in PHPT subjects who attended Department of Endocrinology, Gauhati Medical college and Hospital over last five years (2016-2021). The study was approved by Institutional Ethics Committee of Gauhati Medical College. PHPT was diagnosed based on presence of elevated serum calcium, along with inappropriately raised iPTH (intact Parathyroid hormone). All patients who underwent curative parathyroid surgery with histopathology proven parathyroid adenoma were included. Patients with secondary or tertiary hyperparathyroidism and multiple endocrine neoplasia (MEN) syndrome were excluded.

PHPT subjects were divided into three different age groups i.e., children and adolescent group <18yrs, adult group ≥18-50 years, and older group >50years. All major clinical, metabolic, imaging and postoperative parameters were compared among these groups. Fasting serum calcium, phosphorous, albumin and alkaline phosphatase (ALP) were done on three consecutive days. Calcium was corrected for albumin using the formula, Corrected calcium = Total serum calcium + 0.8(4-Serum albumin). In patients with hypercalcaemia defined as ≥10.2mg/dl, iPTH level was estimated. Hypercalciuria was defined as 24 hour urinary calcium levels more than 4mg/kg body weight. Serum iPTH [Coefficient of variation(intraassay and interassay)- <5%)] and 25(OH)Vitamin D3 were measured 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), lipid profile and haemoglobin were measured by autoanalyzer. (Vitros 5600 Integrated Analyser).

Fasting plasma glucose and post prandial plasma glucose were measured by glucose oxidase method. Skeletal survey was done in all patients to look for bone disease. Ultrasonography (USG) Abdomen and / or x ray abdomen was done to screen for nephrocalcinosis and nephrolithiasis. 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. Technetium (Tc-99) Sestamibi scan done in selected cases.

Postoperatively histopathological examination of parathyroid adenoma was done in all patients. Postoperative iPTH, serum calcium, phosphorus, ALP, 25(OH)Vitamin D3 levels were measured within

first two weeks of postoperative period. Success of surgical procedure was defined as fall in plasma iPTH levels fall by more than 50% and normalization of serum calcium during postoperative period. Symptomatic or biochemical hypocalcaemia was defined as level <8.4mg/dl. Hungry bone syndrome was defined as rapid, profound, and prolonged hypocalcemia associated with hypophosphatemia, hypomagnesaemia and elevated alkaline phosphatase levels. For analysis of association between categorical variables "Chi Square test" was used and for continuous variables "One way ANOVA" was used.

Results

There were 31 consecutive PHPT cases presenting to us over a period of five years. Mean age of the subjects was 38.6±16.3 years with almost similar proportion of female to male subjects (16:15). A total of 6 patients (19.3%) were in children and adolescent group, 16 patients (51.6%) were in adult group and 9 were in older group (27.2%). The duration of symptoms varied from 1month to 72months with average duration of 21.6±19.2 months. The most common presenting manifestation of all patients(n=31) were bone pain and renal stones followed by gastrointestinal and neuromuscular manifestations. [Table 1]. CT neck was able to detect parathyroid lesion in most patients(28/31) in our study. Left inferior parathyroid region was seen to be the common site for adenoma.[Table 2].

Bone pain (p=0.05) as presenting manifestation was seen mainly in the adolescent group(100%) and bony deformity in the form of rickets was seen only in the adolescent group(p=0.001). None of the patients in adolescent group had renal stones and gall stones. Prevalence of renal disease including renal stones(p=0.002) and increased creatinine(p=0.02) were higher in adult group(81%) and gastrointestinal symptoms(p=0.02) in older age group(100%). Intact parathyroid hormone(p=0.01) and alkaline phosphatase(p=<0.001) levels were high among children and adolescent group, whereas increased plasma fasting(p=0.02), and postprandial glucose(p=0.005) were seen in old group(p=0.005). There was no significant statistical difference in other bone deformities including kyphoscoliosis and vertebral collapse, fracture rate, brown tumors (P=0.2), neuromuscular manifestations and other symptoms among different age groups. There was no difference in levels of serum calcium, phosphate, urinary calcium, 25(OH) vitamin D, lipid profile, haemoglobin and postop iPTH among different age groups.[Table 3 & 4, Graph-A].

Postoperative hypocalcaemia across all the age groups developed in 70.9% of the patients, and most were symptomatic with presentation less than 48hours. Hungry bone syndrome (HBS) developed in 41.9% of cases requiring prolonged calcium gluconate infusion, although most of the cases recovered within two weeks, but for a few patients it varied between 1 to 3months. In our patients we did not have other surgical related complications including surgical failure, symptomatic hematoma, wound infection and recurrent laryngeal nerve injury. There was no mortality in our series.

Table I- Presenting characteristics of PHPT subjects (n=31)

Clinical presentation	n (%)
Skeletal manifestations Bone deformity Bone pain Fracture	19(61%) 7 (22.5%) 19 (61.2%) 4 (13%)
Neuromuscular manifestations Proximal myopathy Fatigue	 15 (48%) 14 (45%)
Psychiatric manifestations	2 (6%)
Renal stone	19 (61%)
Gastrointestinal manifestations*	17 (55%)
Pancreatitis	5 (16%)
Gall stones	4 (13%)
Haematological manifestations	18 (58%)
Hypertension	5 (16%)

^ Include all manifestations pertaining to bone

*Anorexia/ nausea/ vomiting/ constipation/ non-specific abdominal pain

Table II- Preoperative biochemical and Imaging parameters and postoperative complications (n=31)

Biochemical parameters	Mean ± SD	Reference range
Serum Calcium (mg/dl)	12.3±1.0	8.4-10.2
Serum Phosphorous (mg/dl)	2.7±0.4	2.5-4
Serum Alkaline Phosphatase (U/L)	1071.7±1320.8	38-126
Parathyroid hormone (pg/ml)	924.4±715.4	15-65
Serum Creatinine (mg/dl)	1.2±0.6	0.66-1.25
25(OH)Vitamin D3 (ng/ml)	21.2±11.0	>30= Normal
Hypercalciuria (mg/24hrs)	299.19±163.3	>4mg/kg
Haemoglobin (g/dl)	11.13±1.97	
Fasting Plasma Glucose (mg/dl)	91.67±13.5	
Postprandial Plasma glucose(mg/dl)	136.1±29.8	
Total cholesterol (mg/dl)	166.1±17.87	
HDL (mg/dl)	48.9±4.8	
LDL (mg/dl)	82.9±23.1	
Triglycerides(mg/dl)	171.2±54.1	
Postoperative PTH(pg/ml)	60.9±38.0	
Preoperative localization of parathyroid adenoma	Sensitivity (n)	
Ultrasound neck	74% (23/31)	
CT neck and thorax	90% (28/31)	
Sestamibi scan	80% (12/15)	
LIPA	48% (15/31)	
Post operative complications	Percentage	
Hypocalcemia	70.9%	
Hungry bone syndrome	41.9%	

HDL-High Density Lipoprotein, LDL-Low Density Lipoprotein, LIPA- Left Inferior Parathyroid Adenoma

Table III Presenting characteristics of PHPT subjects among different age groups

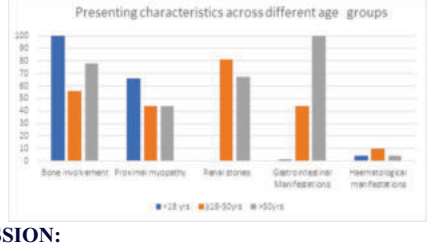
Age group (years)	<18 (n=6) Mean ± SD or n(%)	≥18-50 (n=16) Mean ± SD or n(%)	>50 (n=9) Mean ± SD or n(%)	P value
Mean age(years)	15.3±1.6	36.4±6.9	58.2±7.1	<0.001
Symptoms duration (months)	24±14	40.6±57.6	10.4±10.7	0.33
Female(%)	5(87)	6(38)	5(56)	0.15
Rickets	3(50)	0	0	0.001
Bone deformities (Vertebral collapse &/or kyphoscoliosis)	2(33)	3(19)	1(11)	0.5
Bone pain	6(100)	8(50)	4(44)	0.05
Fracture	2(33)	2(13)	0(0)	0.17
Brown tumours	2(33)	3(19)	1(11)	0.56
Fatigue	1(16)	9(56)	4(44)	0.25
Proximal muscle weakness	4(66)	7(44)	4(44)	0.6
Psychiatric manifestations	1(17)	1(6)	0(0)	0.44
Gastrointestinal*	1 (17)	7(44)	9 (100)	0.02

Renal stone	0(0)	13 (81)	6(67)	0.002
Gallstone	0(0)	2 (13)	1 (11)	0.66
Pancreatitis	1(17)	3 (19)	0 (0)	0.38
Haematological	4(67)	10(63)	4(44)	0.6
Hypertension	0(0)	3(19)	2(22)	0.47

Table IV Preoperative biochemical and Imaging parameters and postoperative complications among different age groups

Age group (years)	<18 (n=6) Mean ± SD or n(%)	≥18-50 (n=16) Mean ± SD or n(%)	>50 (n=9) Mean ± SD or n(%)	P value
S. calcium (mg/dl)	12.4±0.48	12.3±1.2	12.3±0.9	0.9
S. phosphate (mg/dl)	2.7±0.5	2.6±0.4	2.8±0.4	0.24
S. ALKP (IU/L)	2732.5±1445.4	814.8±1134.8	443.33±369.33	0.0006
iPTH (pg/ml)	1668.5±409.7	772.9±666.6	790.2±680.4	0.014
Hypercalciuria (mg/24hrs)	352.3±151.8	339.5±174.4	227.4±116.3	0.19
25 (OH) Vitamin D3 (ng/ml)	18.6±12.4	21.3±10.3	20.4±8.3	0.68
S. creatinine(mg/dl)	0.6±0.24	1.38±0.7	1.26±0.28	0.02
Total Cholesterol(mg/dl)	148.8±8.3	170.5±18.5	170.4±13.9	0.06
HDL (mg/dl)	51.5±0.95	49.5±4.84	46.22±5.1	0.1
LDL (mg/dl)	71.7±7.84	84.0±29.5	88.6±12.03	0.4
Triglycerides (mg/dl)	127.8±9.0	183.6±61.03	177.09±43.06	0.9
Fasting Plasma Glucose(mg/dl)	83.3±6.1	89.13±7.5	96.2±10.65	0.02
Postprandial Plasma Glucose(mg/dl)	106.1±7.2	130.9±10.8	143.1±31.5	0.005
Haemoglobin (g/dl)	10.53±2.57	11.13±1.83	11.5±1.6	0.63
LIPA	3(50)	7(44)	5(56)	0.8
Post operative PTH(pg/ml)	72.16±20.07	57.18±46.08	65±36	0.73
Postop Hypocalcemia	5(83)	11(69)	4(44)	0.25
Hungry Bone syndrome	4(67)	6(38)	2(22)	0.21

Graph A-



DISCUSSION:

The present study is one of the few studies done on PHPT with respect to its presentation in different age groups. The age of presentation of PHPT in our study was (38.6±16.3) years which is in concordance with study done by Shah VN et al. and Jha S et al., where the mean age in them was 38 years.[13,14] Studies by Mallikarjuna VJ et al and Mithal A et al. reported a higher incidence of age of presentation(48 years).[15,16] This clearly resonates the fact that Indian population presents relatively at an early age compared to western population(5th to 6th decade).[17] In the present study adult group(19 to 50 yrs) were in higher number which is similar to a study by Shah VN et al (25 to 50yrs).

In discordance to studies by Mithal A et al, Jha S et al., Priya G et al. , where higher female predominance seen (>2:1), in our study we found an almost equal gender distribution.[14,16,18] In our study adolescent age group had higher female predominance which is in contrast to a study by Oltmann SC et al. where higher female predominance was seen in older group.[19] The mean lag time of presentation of PHPT in our study was relatively earlier(21 months) when compared to other Indian studies.[14,18,20] Although duration of presenting symptoms was higher in adult group(40.6±57.6), but it was not statistically significant.

The most common clinical presentation were skeletal manifestations (including bone pain, fracture, deformities) which is in accordance with other Indian studies. [16,18,20] Common clinical manifestation in adolescent age group was bone pain which was seen in all patients as compared to 44-50% in the other two groups. Rickets as presenting manifestation was seen only in adolescent group(p-0.001) which is in concordance with similar study from India.[13] Renal stones and gall stones were not seen in children and adolescent group, whereas renal stones were significantly higher in adult group(p-0.002) and gastrointestinal manifestations were more prevalent in older group(p-0.02). In a study by Shah VN et al renal stones was significantly higher in adult group and gastrointestinal symptoms were higher in the same age group but were not statistically significant. Whereas the rest of clinical manifestations including neuromuscular symptoms, pancreatitis, gall stones and others were not significant among different age groups which is in agreement with a study by shah VN et al.[13]

In our study iPTH levels was higher in adolescent group which is in discordance to a study done by Oltmann SC et al., where higher levels was seen in older group.[19] Whereas similar studies by Shah VN et al and Kandil E et al., did not showed significance across age groups in the levels of iPTH.[13,21] Levels of serum ALKP was higher in adolescent group which is supported by other studies in India.[12,22], this could be due to aggravation of physiological higher osteoblastic activity and increase bone growth that occurs during this period. Levels of serum calcium, phosphorus and 25(OH)Vitamin D did not differ significantly between age groups which is in well concordance with Shah VN et al study, whereas similar other studies showed significant higher calcium levels and lower Vitamin D levels in younger age group compared with other groups although the age group division in these studies were different.[19,21]

The most common site of adenoma in our study was Left inferior parathyroid gland (48%) which is in agreement with studies in India.[14,20] In a study from north India reported right inferior parathyroid adenoma as commonest site (50%).[16] Further in our study LIPA was the common lesion across all age groups. In the present study CT neck was able to detect lesion in maximum number of subjects when compared with other imaging modalities which is supported by other Indian studies.[20,23] Although not significant, higher post operative iPTH levels were noted in children and adolescent group, but there is a greater degree of percentage drop in iPTH level in this group. In contrast to our finding a study by Oltmann et al, reported patients with >50year age group to have higher parathyroid hormone levels at the time of postoperative visit, 1 to 2 wk after surgery.[19]

In our study most of the subjects had postoperative hypocalcemia (71%) which was managed by oral calcium and calcitriol with or without requirement of calcium gluconate infusion. Hungry bone syndrome was seen in 42 percent of our subjects which is almost similar to a study done by Bhansali A et al. [20] Misgar et al, and Muthukrishnan et al, reported lower rate of HBS in 10.12% and 9.8% of the subjects respectively.[24,25] Although not significant, higher proportion of patients in adolescent group in our study had higher postoperative complications including hungry bone syndrome and hypocalcaemia, this might be due to increased skeletal manifestations and higher preoperative ALKP concentrations reflecting increased bone turnover in this group.[26]

CONCLUSION:

In our study age has substantial influence on PHPT presentation. Bone pain and deformity was common in adolescent group. Renal disease and gastrointestinal manifestations were common in adult and older group respectively. Alkaline phosphatase and iPTH levels along with postoperative complications were higher in adolescent group.

Limitations of our study were being smaller sample size, lack of data on intraoperative monitoring of iPTH levels, adenoma weight and Bone mineral density.

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