ORIGINAL ARTICLE

Primary Hyperparathyroidism in Saudi Arabia: A Review of 46 Cases

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SUMMARY

Records of 46 patients who were treated for primary hyperparathyroidism at King Khalid University Hospital, Riyadh Saudi Arabia from 1st July 2000 to 30th June 2006 were reviewed. Mean age at diagnosis was 44 years (range 13 – 70 years) and average duration of symptoms was 39 months (1 month to 11 years). There were 35 females and 11 males with a ratio of 3.2:1. Bone pains were the major symptoms at presentation in 45.7% followed by no symptom in 23.9%, renal stones in 15.2%, polyuria in 6.5%, while 4.3% each presented with depression, and constipation. Males had significantly more severe disease with higher serum calcium, higher urinary calcium excretion, and higher serum creatinine. Ninety six percent of patients had successful surgery and 4% (two patients) each had recurrence and hungry bone syndrome. It is concluded that PHPT in Saudi Arabia continues to be a symptomatic disorder with skeletal and renal manifestations occurring at a younger age and males having more severe disease. Further prospective studies are needed to verify our findings.

KEY WORDS:
Primary hyperparathyroidism, Clinical features, Saudi Arabia

INTRODUCTION

Primary hyperparathyroidism (PHPT) is recognised worldwide. Its prevalence however varies. For instance PHPT has been reported to be common in developed countries with hospital based studies as high as 1600 cases in 16 years [1,2]. In contrast hospital based figures quoted from developing countries are much lower. For example 52 cases of PHPT were recorded in 13 years from India[3], 115 cases in 20 years from Brazil[4], and 41 cases were seen over a decade in Jordan[5]. The relatively low prevalence of PHPT in developing countries was attributable to underreporting or under diagnosis where calcium investigation is infrequent[6,7]. Studies on PHPT in the Kingdom of Saudi Arabia, a third world country where routine calcium test was introduced in hospitals in the year 2000 were few and mainly concentrated on specific aspects of PHPT such as its impact on pregnancy[8], surgery [9] or clinico-pathological features[10]. There is no recent study to our knowledge devoted to assess overall pattern of PHPT in the kingdom. The aim of the study was therefore, to determine the mode of presentation, biochemical features, and treatment outcome of patients with primary hyperparathyroidism in Saudi subjects.

MATERIALS AND METHODS

The study was conducted at King Khalid University Hospital (KKUH) Riyadh on patients who satisfied the inclusion criteria highlighted below. Approval for laboratory and clinical review was obtained from the ethics committee of KKUH. This large tertiary centre caters for patients referred from all over the Kingdom. All hospital admissions were recorded electronically by the same medical record staff using codes according to the international classification of diseases (ICD). Data of patients admitted at the hospital with hypercalcemia and proven biochemically to have PHPT during the period 1st July 2000 to 30th June 2006 were retrieved from the record. We also reviewed the following data: age, sex, presenting signs and symptoms as well as duration of symptoms prior to presentation, routine biochemical investigations, radiological findings, histopathological diagnosis and post surgical course. The diagnosis of PHPT was based on two or more of the following criteria: 1. persistent elevation of serum calcium above the upper limit of normal range of 2.55 mmol/l excluding other demonstrable causes of hypercalcemia; 2. increased circulatory immunoreactive intact parathyroid hormone (PTH) above the upper limit of normal range of 6.9 pmol/l; 3. characteristic radiologic features of PHPT; and histological evidence (after parathyroidectomy) of parathyroid adenoma. Patients with a suggestion of multiple endocrine neoplasia, secondary and tertiary hyperparathyroidism or with incomplete record were excluded from the study.

Fasting blood samples were collected on three consecutive days for estimation of serum total calcium, inorganic phosphorus, total serum alkaline phosphatase, albumin and creatinine. All calcium values were corrected for respective serum albumin concentrations. Twenty-four hour renal excretion of calcium and phosphorus were used as additional helpful tests to complete the biochemical profile. The serum and urine chemistry were determined by multichannel autoanalyser in the central hospital laboratory with an intra-assay coefficient variation <4%. PTH and 25-hydroxycholecalciferol were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA) with intra-assay and inter-assay coefficient of variation less than 2% and 5% respectively. In addition, bone scan was done in some patients to look for the extent of bone involvement. Imaging of the neck included one or more of the following: ultrasonography, contrast enhanced computerised tomography, and parathyroid scan, either a thallium-technetium subtraction study or sestamibi scan, whenever indicated. Bone mineral densities (BMD) of

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femoral neck and lumbar spine (L2-L4) were performed by dual x-ray absorptiometry (Lunar Radiation Corp, Wisconsin). Normal BMD ranges were 1.143±0.105 g/cm^2 for the lumbar spine and 0.959±0.100 g/cm^2 for the femoral neck for Saudi women (age 20-40 years) peak bone mass as previously described [11].

Parathyroidectomy was performed under general anesthesia. Depending upon the radiological findings, the four parathyroid glands were evaluated grossly before determining the extent of resection. If a single gland disease was present, the enlarged gland was removed and sent for further studies. If more than one gland was involved, then all the diseased glands were resected and sent for histopathological analysis.

Data were expressed as mean ± SEM. In addition to descriptive statistics, the chi-square test was used for comparison between categorical variables and Student's t test was used in comparing continuous variables. In a case where the data was not normally distributed, an appropriate non-parametric test was used for comparison. Other tests used included one-way analysis of variance (ANOVA). All t values were calculated as two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

Table I shows the clinical and biochemical features of patients with primary hyperparathyroidism seen at King Khalid University Hospital Riyadh between July 2000 and June 2006. The mean age at presentation was 44 years with 95% confidence interval for the mean at 39.7-48.9 and a range between 13 and 70 years. Duration of symptoms before presentation also varied between one month and 11 years, with an average of 39 months. All the patients had serum calcium above the normal range with normal or high serum parathyroid hormone (mean 44 pmol/l; range 6.2 – 189).

Table II depicts differences in the clinicopathologic characteristics of patients with primary hyperparathyroidism based on gender. In all, 11 males representing 24% and 35 females (76%) with male: female ratio of 1: 3.2 were seen. Males had significantly higher serum calcium level 3.4 ± 0.3 mmol/l as compared to females 2.9 ± 0.1 mmol/l (p = 002). Serum creatinine level was also significantly higher in males than in females 152 ± 35 mmol/l vs 60 ± 4 mmol/l (p = 0.0003). In addition, the 24-hour urinary calcium excreted was also higher in males than in females, 19 ± 12 compared to 6 ± 1 in females, $p < 0.05$. Other variables were similar in both sexes.

Table III represents the major clinical symptoms of patients with primary hyperparathyroidism. The majority of patients presented with bone aches (45.7%). Other findings at presentation included renal stones (15.2%), polyuria (6.5%), constipation and depression (4.3%). 23.9% of patients were asymptomatic at the time of diagnosis.

Radiological imaging for localization revealed TL-Tc/Sestamibi to have correctly detected parathyroid adenoma in 32 out of 36 patients with a sensitivity of 88.9%, CT scan 11 out of 12 patients giving a sensitivity of 91.6%, ultrasound 13 of 17 patients (76% sensitivity). Bone scan showed generalized increased uptake in 8 out of 24 patients tested while DXA scan showed osteopenia/osteoporosis in 83% of patients and normal BMD in 16.6%.

All patients underwent parathyroidectomy. Two patients developed hungry bone syndrome which was effectively managed and two patients had recurrence of the disease after the surgery.

Table I: Clinical and biochemical characteristics of patients with primary hyperparathyroidism

Parameter	Mean + SEM	Range
Age (years)	44.3 ± 2.3	13 - 70
Duration (months)	39.4 ± 6.5	1 - 132
Serum calcium (mmol/l)	3.0 ± 0.1	2.6 - 5.3
Serum phosphorus (mmol/l)	0.8 ± 0.1	0.3 - 2.3
Serum parathyroid hormone (pmol/l)	44.0 ± 6.6	6.2 - 189
Serum alkaline phosphatase (IU/l)	473 ± 146	66 - 5515
Serum creatinine (umol/l)	87.6 ± 12.8	35 - 402
Serum 25 hydroxy cholecalciferol (nmol/l)	35.8 ± 8.6	5.0 - 70.0
24-hour urinary calcium (mmol/d)	8.2 ± 2.3	0.3 - 43.3
24-hour urinary phosphorus (nmol/d)	14.0 ± 4.2	0.8 - 32.7

Table II: Clinical and biochemical features of patients with primary hyperparathyroidism according to gender

Parameter	Male (11)	Female (35)	p value
Age (years)	39 ± 5	46 ± 3	0.2
Duration (months)	41 ± 13	39 ± 8	0.9
Serum calcium (mmol/l)	3.4 ± 0.3	2.9 ± 0.1	0.002
Serum phosphorus (mmol/l)	0.9 ± 0.2	0.8 ± 0.1	0.3
Serum alkaline phosphatase (IU/l)	242 ± 69	543 ± 189	0.4
Serum chloride (mmol/l)	110 ± 2	108 ± 1	0.2
Serum sodium (mmol/l)	141 ± 1	141 ± 1	0.9
Serum urea (mmol/l)	10.8 ± 5	4.1 ± 1	0.06
Serum creatinine (mmol/l)	152 ± 35	60 ± 4	0.0003
Serum parathyroid hormone (pmol/l)	50 ± 9	42 ± 8	0.6
24-hour urinary calcium (mmol/d)	19 ± 12	6 ± 1	0.03

Table III: Clinical presentation of patients with primary hyperparathyroidism

Signs/symptoms	Number (%)
Bone aches	21 (45.7)
Asymptomatic	11 (23.9)
Renal stones	7 (15.2)
Polyuria	3 (6.5)
Constipation	2 (4.3
Depression	2 (4.3)

DISCUSSION

We have shown that the clinical picture of PHPT in Saudi Arabia is similar to that seen previously in the West [12]. Notably, the disease is seen in relatively young patients with demonstrable organ involvement at presentation in the form of skeletal or renal disease or both. With 50% of patients below the age of 50 years, we found that the mean age at presentation of PHPT was a decade younger than that described in reports from Caucasian series where mean age at presentation of patients with PHPT is reported from 55 years to 62 years [6, 13], but consistent with other reports from developing countries [4, 14]. It is not clear why our subjects present at a younger age although vitamin D deficiency which is common in third world countries was thought to be responsible [15, 16]. However, in our series, of the eight patients tested for vitamin D levels, two were found to have low serum levels representing 25% of the patients, in keeping with the previous findings in the region showing high prevalence of nutritional hypovitaminosis D in the community[17] but differ from the report of others [3].

An interesting finding in our study was the emergence of a subclass of patients at presentation with no symptoms of hyperparathyroidism. We have reported from the same hospital a decade ago when calcium investigation was not included in the routine assessment of subjects seen at clinics [10]. At the time, all the patients were diagnosed based on symptoms at initial visit. Similar observations of increasingly diagnosed asymptomatic subjects with PHPT in developing countries were made [18, 19] which might lead to an overall increase of PHPT in the local population [20, 21]. Currently, over 60% of patients with PHPT in the developed world are diagnosed without any symptoms[22, 23]. In our study, about a quarter of the patients were diagnosed following abnormal laboratory result of calcium. Although PHPT is still largely symptomatic disease in Saudi Arabia, the picture is shifting from uniformly severe symptomatic disease observed earlier [7, 10] to no clinical symptom at the time of presentation which we believe could be due to the introduction of routine automated calcium assays in hospital practice. However, it is important to note that there is a limitation to retrospective studies in general. Observations derived from such studies may contain some missing information. The present work must be interpreted in the knowledge of the defects inherent in such studies. Nevertheless, our result is in agreement with other reports[4, 19].

Bone pain accounted for 45.7% of our subjects with PHPT at presentation with osteopenia/osteoporosis in 83% of patients tested with DXA. In addition, 15.2% of the patients had kidney stones at the time of initial visit. This clearly showed 60% of the patients came with bone or renal disease as described in other developing countries [4, 5]. In a landmark study, Silverberg reported a change in prevalence of bone disease in patients with PHPT in Caucasians with radiologically demonstrable pathology currently seen in less than 2% as against 23% a decade earlier when routine calcium check up was not implemented [24]. Similarly Heath noted a dramatic fall of renal stone prevalence following introduction of routine calcium measurement in his subjects from 57% to less than five percent in recent years [25].

Primary hyperparathyroidism was also found in our study to be more common in females than males with a ratio of 1: 3.2 as observed in the West as well as from other third world countries [9, 26]. However, despite the relative rarity of the disease amongst males, it was shown from our data to be more severe at presentation than in females. This was demonstrated by highly significant hypercalcemia, and organ involvement in the form of marked hypercalciuria and renal impairement. The reason for this finding is not clear. A possible explanation though not supported by our data is the frequent hospital visits by females during their reproductive lives as for instance during pregnancy during which they are often being routinely subjected to a series of investigations including serum calcium[8]. However, there was no gender significant difference in duration of symptoms prior to presentation possibly due to the small number of subjects studied. Furthermore, the less severe PHPT in females might be due to hormonal protection from the effect of hypercalcemia during the reproductive period with hyperestrogenemia as noted by Carling and colleagues [27]. However, in our series, severe PHPT was not observed in postmenopausal women who presumably have low serum estrogen levels. Furthermore, we did not measure estrogen levels in our cohort, as it was not included as part of the work up for patients with PHPT.

Parathyroid adenoma can be located in unusual sites such as retroesophageal, intrathyroidal, lateral neck and mediastinum [28]. Because of potential difficulties in correctly locating abnormal parathyroid tissue, preoperative approaches have been developed. We recognised that for a experienced parathyroid surgeon, localization of the abnormal gland is superfluous. Notwithstanding, most of our patients were subjected to non-invasive imaging to assist the surgeon in the operative care. These included ultrasound, computed tomography, technetium-99m (Tc-99m) sestamibi, and technetium subtraction study. In our study, Tc-99m (Tc-99m) sestamibi procedure showed a high diagnostic yield with 89% sensitivity as reported elsewhere[29]. On the other hand, being cheap and readily available in typical developing countries, ultrasound showed a promising diagnostic tool in PHPT in which we reported a sensitivity of 76% similar to the findings of other investigations [30].

All our patients were subjected to bilateral neck exploration with resection of enlarged parathyroid glands. Although the procedure was performed by more than one parathyroid surgeon, we recorded a success rate of 96% and only two patients had recurrence in an experience similar to that of others[31]. Furthermore, post surgical complication in the form of hungry bone syndrome occurred in only two of our patients and responded well to treatment. The relative rarity

of hungry bone syndrome in our series is not clear. For instance Bhansali *et al*., reported a 50% incidence of hungry bone syndrome in Asian subjects despite preoperative calcium and vitamin D supplementation. In our series, preoperative hypercalcemia was managed conservatively and with intravenous zolidronate if it failed to respond to diuretic and high fluid intake. None of our patients took calcium and vitamin D prior to surgery yet we infrequently observed hungry bone syndrome possibly due to the protective effect of bisphosphonate as reported in the recent literature [32].

CONCLUSION

We have demonstrated PHPT in Saudi patients to be a mainly symptomatic disease with skeletal and renal manifestations occurring at a younger age as in developing countries. An appreciable number of subjects though were asymptomatic at diagnosis. We have in addition, shown that although fewer males than females had PHPT. Severe form of the disease was noted in the former. Further prospective studies on a larger population are needed to clarify our findings.

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