Primary hyperparathyroidism

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ABSTRACT

Objective: The aim of the study is to present the clinical pattern, surgical indication and management of primary hyperparathyroidism in a teaching hospital in the Kingdom of Saudi Arabia (KSA).

Methods: The records of patients who underwent surgical treatment for primary hyperparathyroidism at the King Khalid University Hospital, Riyadh, KSA from March 1992 to October 2002 were reviewed for epidemiological data, biochemical, radiological investigation, operative procedures, histopathology result, preoperative localization studies included neck ultrasonogram, neck computerized tomography and thallium-technetium subtraction scan. All patients underwent surgery under general anesthesia and procedures were bilateral, unilateral neck exploration, or minimal invasive parathyroidectomy.

Results: A total of 41 patients with diagnosis of primary hyperparathyroidism were reviewed. There were 30 females and 11 males with a mean age of 42 years (range 14-78 years). The musculoskeletal symptoms were the major symptoms in 30 patients (73%) followed by renal stone in 6 patients (14.6%), peptic ulcer in 2, acute pancreatitis in one, asymptomatic patients accounted for 5% (2 patients) and the thallium-technetium scan has the highest sensitivity rate (89%) among the preoperative localization studies. The histopathological results showed adenoma in 36 cases (87.8%), hyperplasia in 3 cases (7.3%) and no pathology found in 2 cases.

Conclusion: Almost all the patients presented with late symptoms and complications of primary hyperparathyroidism, the number of asymptomatic patients, is low due to lack of routine serum calcium check up. Owing to the high sensitivity of thallium-technetium scan and the relatively low incidence of hyperplasia (7.3%), we believe that unilateral neck exploration guided by preoperative scan is a suitable procedure for primary hyperparathyroidism.

Saudi Med J 2003; Vol. 24 (11): 1214-1218

Primary hyperparathyroidism (PHPT) is caused by overproduction of parathyroid hormone (PTH) by one or more parathyroid glands that usually result in hypercalcemia. The disease is common in the western with a prevalence rate of one per 1000 population.[1] The 2 available reports from Kingdom of Saudi Arabia (KSA) indicate the low prevalence of the disease.[2,3] The clinical pattern and surgical indications changed dramatically with time from an advanced and complicated disease in the 1950s and 1960s,[4,5] to a totally asymptomatic form discovered by a high serum calcium level during routine checkup or as a screening test in patients with osteoporosis. The surgical treatment has evolved as well from a standard bilateral to unilateral exploration and recently toward minimal invasive and radio guided parathyroidectomy. Our study presents the pattern and management of PHPT in a teaching hospital in the KSA over a 10 years period.

Methods. The medical records of patients admitted to the King Khalid University Hospital, Riyadh, KSA with diagnosis of PHPT, who underwent surgical treatment from March 1992 to October 2002 were retrospectively reviewed for age, sex, clinical presentation, biochemical and radiological

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Received 6th April 2003. Accepted for publication in final form 16th June 2003.

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investigation, surgical management and histopathology results. There were 41 patients. The diagnosis of PHPT was made in patients with elevated serum calcium level of >2.6 mmol/l (normal range 2.1-2.55 mmol/l) and elevated PTH (normal range 12-72 pg/ml) and presence of either parathyroid adenoma or hyperplasia upon surgical exploration. The laboratory tests include serum calcium level, phosphorus, PTH, alkaline phosphatase, 24 hours urine collection analysis for calcium, radiological investigations included musculoskeletal survey, bone mineral density (BMD) in lumbar region and femur neck and bone scan. The preoperative localization studies included ultrasonogram (USG) and computerized tomography (CT) of the neck and thallium-technetium subtraction scan. All the patients underwent surgery under general anesthesia; the procedures were either unilateral, bilateral exploration of the neck, or minimal invasive parathyroidectomy (MIP). Patients with one enlarged gland (adenoma) had a removal of affected gland, and in some patients, the other glands were biopsied. The patients with 4 enlarged glands underwent subtotal parathyroidectomy and frozen section were performed in all cases. Postoperatively, patients were reviewed for serial serum calcium level, complications and follow up in outpatient clinic with calcium level. The final histopathological reports were reviewed.

Results. A total of 41 patients with diagnosis of PHPT were reviewed. There were 30 female and 11 male patients with a female to male ratio of 3:1 and a mean age of 42 years (range 14-78 years). The majority of our patients; 78% (n=32) were ≤50 years and 22% (n=9) were >50 years, 23 patients (56%) presented in fourth and fifth decades, and the peak incidence was in the fourth decade. The majority (56%) was in the fourth and fifth decade. Thirty-nine patients presented with significant and late symptoms of PHPT. The musculoskeletal symptoms were the major symptoms in 30 patients (73%) (weakness in 16, generalized bone pain in 19, fractures in 8, osteolytic lesions in 5, and brown tumors in 5), followed by renal stones and nephrocalcinosis in 6 patients (14.6%), peptic ulcer in 2 patients, one patient with acute pancreatitis, and only 2 patients in this study were operated for asymptomatic PHPT. The first patient has a significant high serum calcium level 3.2 mmol/l and the second patient had a papillary thyroid cancer and the hypercalcemia was incidentally detected preoperatively. He underwent parathyroidectomy simultaneously with total thyroidectomy. The PHPT was a part of multiple endocrine neoplasm-type I (MEN-I) syndrome in 2 patients. The first patient has pituitary adenoma detected by CT scan of the brain and the second has pituitary adenoma and gastrinoma; they developed recurrence of hyperparathyroidism 2 years after the initial surgery (removal of parathyroid adenoma).

The high serum calcium level was detected in 40 patients (97,5%), ranging from 2.6-4.2 mmol/l. Parathyroid hormone level was raised in all patients (range 96-3157 pg/ml). The alkaline phosphatase was raised in 19 patients (46%). The low phosphorus level was detected in 28 patients (68%). The calcium level in 24-hours urine collections was high in 14 patients (34%). The musculoskeletal survey showed bone abnormalities in 28 patients (68%). Fractures in 8 patients, osteolytic lesions in 5, brown tumor in 5, subperiosteal erosions in 8, and marked osteopenia in 16 cases. The bone scan was performed in 27 patients and showed evidence of osteopenia in 20 patients (48%). The bone mineral density was performed in 23 patients and it was abnormal in 20. The neck ultrasound was performed in 19 patients and enlarged parathyroid gland were detected in 9 cases with sensitivity of 47%. The neck CT scan was performed in 22 patients with sensitivity and localized the abnormal glands in 15 cases (68%). The thallium-technetium scan was carried out in 37 patients and it was able to localize the enlarged gland in 33 cases with sensitivity (89%). All patients underwent neck exploration under general anesthesia. Sixteen patients had bilateral neck exploration, and 21 underwent unilateral exploration, and in the latest 2 years of the study, 4 patients had a MIP. Frozen section of the removed glands were carried out in all cases and identification of abnormal glands were possible in 39 cases (95%). The overall postoperative complications were hypocalcemia in 26 patients (63%). All returned to normal level except one patient continue to have permanent hypocalcemia (2.4%). Recurrent laryngeal nerve (RLN) injury in one case (2.4%). Esophageal injury in one treated by reexploration and primary repair, wound hematoma in one (2.4%), both RLN and esophagus injuries occurred in one patient following bilateral neck exploration. Postoperatively, 39 patients have their serum calcium level returned to normal immediately after surgery with a success rate of 95%. However, 12 patients were discharged on oral calcium and Vitamin D (Vit. D) supplement postoperative as they had severe osteoporosis and to be followed by our endocrinologist. One patient with MEN-I syndrome continue to have persistently high calcium level after negative bilateral neck exploration, this patient had a unilateral neck exploration and removal of adenoma 4 years earlier, the other patient had bilateral neck exploration and biopsies of the removed glands showed normal parathyroid tissues. Thirty-six patients have regular follow up in the outpatient clinic with a mean of 28 months (range 5-97 months). Two patients developed recurrence of hyperparathyroidism, the first patient developed recurrent hyperparathyroidism after 2 years and he underwent neck reexploration (bilateral) and removal of adenoma. The second (with MEN-I) developed recurrence after 4 years and had a negative bilateral neck exploration, and finally referred to specialized center.

The analysis of histopathology results showed a parathyroid adenoma (chief cell adenoma) in 36 cases (87.8%), hyperplasia in 3 cases (7.3%) and in 2 cases (5%); no pathology was detected in the removed glands. There was no case of carcinoma in our study.

Discussion. The prevalence of the disease is approximately one per 1000 and approximately 100,000 new cases of PHPT are identified each year in the United States of America.[1] In KSA, there is no available data on prevalence of the disease, however, Fouda[2] reported a prevalence rate of 11.34 per 100,000 hospital admission, which include 24 patients during a period of 15 years. The other report from KSA is from Asir region, reported 13 cases only during 10 years period from all hospitals, which serve 1.2 million population.[3] In the Western, the PHPT occur usually between the age of 15-65 years, the peak incidence is in the fifth to sixth decade of life with a female to male ratio of approximately 3.5:1.[6] Interestingly, most of our patients 56% (**Table 1**) were in the fourth and fifth decades and the peak incidence in our study was in the fourth decade (31%). This significant difference from Western studies may need further workup to be explained. Since Mandl[7] performed the first successful parathyroidectomy in 1925 in Austria for patient with PHPT with hypercalcemia and osteitis fibrosa cystica, the classical signs and symptoms (painful bones, kidney stones, duodenal groans, psychic moans and fatigue overtones) were described in 1950 and 1960.[4,5] The indications of surgery for PHPT in our study were the musculoskeletal symptoms in 30 patients (73%), renal stones and nephrocalcinosis in 6 patients (14,4%), acute pancreatitis in one (2,4%), peptic ulcer in 2 (4,8%), and only 2 patients were asymptomatic (4,8%). This results are similar to western surgical literatures in the 1950s and 1960s,[8-11] where all the patients were operated due to the late presentation and complication of the disease, but in mid 1960s the most common form of PHPT was the asymptomatic disease characterized by mild chronic hypercalcemia due to routine measurement of serum calcium level as the facility of multi-channel auto-analyzer appeared.[10,11] Only 2 patients in our study were asymptomatic (4.8%) in contrary to recent western studies where asymptomatic PHPT accounting for 11-14% of surgical indications.[12,13] The other significant difference in western reports is neuropsychiatric symptoms (depression, anxiety, fatigue, concentration difficulties, failing memory), which was the primary indication of surgery in 10% of cases,[12] and the only patient in our study who had depression, underwent surgery due to other associated symptoms. In Udelsman[13] study in 1996, the symptoms and signs in 650 patients operated for PHPT were fatigue in 28%, gastrointestinal in 24%, depression 12%, mental status changes in 24%, renal stones were found in 28%, bone disease in 47%, pancreatitis 2%, and asymptomatic patients 11%. Delbridge[12] has studied the changes in surgical indication over the past 3 decades, they found that renal stones were the main indication (58%) of surgery between 1962-1969, but has progressively decreased with time and accounted for only 15% of surgery for PHPT in the period 1990-1996. The number of asymptomatic patients has increased in 1970s and 1980s, and between 1990 and 1996 the marked changes was the increase in patients with low BMD detected on screening for osteoporosis (31%) followed by neuromuscular and neuropsychiatric 20%, renal calculi 15% and asymptomatic patients 14%. Recent studies showed that the coexistence of Vit. D deficiency in patients with PHPT may put the patient at a significantly higher risk of losing bone mineral density and development of osteoporosis. Igmanson et al[14] studied Vit. D (25 OHD3) in 22 Saudi patients with PHPT to establish whether there was coexisting Vit. D deficiency and osteomalacia. They found that levels (25 OHD3) were below normal in 14 patients and in the low normal range in 7 patients and they concluded that PHPT in KSA seems to be associated with a high frequency of severe bone disease. In country where Vit. D stores are low, this likely to be due to combination of Vit. D deficiency osteomalacia in addition to the effects of the primary disease. A lot of debate exists regarding the value of preoperative localization studies in patients with PHPT. Ultrasonogram has a sensitivity rate of 36-75%.[15-16] Computed tomogram is useful in localization of the ectopic glands especially mediastinal and large tumors with sensitivity rate of 42-68%. Magnetic resonance imaging is preferable to CT, with a better sensitivity rate of 57-88%. The sensitivity of thallium-technetium scan is approximately 73%.[17-19] Our results showed sensitivity rate of 47% for neck USG, 68% for CT and 89 for thallium-technetium subtraction scan. Owing to the significantly high sensitivity rate of thallium-technetium scan in our series, we believe that

Table 1 - The clinical presentation in patients with primary hyperparathyroidism.

Presentation	n	(%)
Musculoskeletal	30	(73)
Fractures	8	
Osteolytic lesion	5	
Bone pain	19	
Weakness	16	
Renal stone	6	(14.6)
Nephrocalcinosis	1	
Peptic ulcer	2	(4.8)
Acute pancreatitis	1	(2.4)
Asymptomatic	2	(4.8)

it should be considered as the first method of diagnostic workup for PHPT, especially when the surgeon planning to do unilateral exploration. However, recently the technetium TC ^{99}mm-sestamibi scanning had replaced thallium–technetium subtraction scanning in most medical centers due to its better resolution and sensitivity 70-91% versus 68-73%.[12,13,15] In 80-85% of cases, PHPT is due to a single adenoma, the double parathyroid adenomas are unusual (2%), and in 12-15% the 4 glands are enlarged (hyperplasia). The carcinoma was accounted for <1% of cases.[20-21] We found a high incidence of single adenoma (87.8%) in our patients, and no case of double adenoma. The hyperplasia was found in 3 cases only (7.3%), and in 2 cases no pathology was detected in the removed glands. The incidence of hyperplasia is relatively lower than the western reports.[20,21] But it is consistent with Udelsman study[13] which reported a rate of 7.5% for hyperplasia and no case of PTH cancer. There is a general agreement that surgery is indicated in all patients with symptomatic PHPT, and in asymptomatic patients with serum calcium levels above 12 mg/dL in patient who are <50 years.[22-23] The surgery of parathyroid gland has developed with the time, historically, the standard operation bilateral neck exploration (exploration of the four glands) when performed by experience endocrine surgeon was associated with cure rates of 95-99% with less than 1-2% complication.[24-26] The cure rate in our study is 95% which seems to be a favorable and similar to recent literatures. As the PHPT is due to single adenoma in 80-85%, several surgeons advocated a unilateral neck exploration guided by preoperative localization studies.[20-22] The availability of intraoperative PTH monitoring to check the adequacy of resection will decrease the need for bilateral approach when the preoperative studies suggest a solitary adenoma.[27-29] More recently many surgeons recommended a minimally invasive parathyroidectomy MIP. The bilateral neck exploration in our study was carried out in 16 patients (39%), unilateral exploration in 21 patients (51%) and recently there is a trend towards MIP. Four patients underwent this procedure in the latest 2 years of the study. The surgical complications include persistent vocal cord paralysis owing to RLN injury or permanent hypocalcemia (1-2%),[24-26] which is similar to our results. However, we had an esophageal injury, which is a rare complication of parathyroid surgery.

In conclusion, most of our patients presented with advanced and complicated PHPT, the number of asymptomatic patients is very low, owing to lack of routine calcium measurement, the primary care physician should be addressed and encouraged to include calcium in the routine laboratory checkup list. All patients with PHPT should have Vit. D level assessment in order to exclude the coexistence of Vit. D deficiency with PHPT. Primary hyperparathyroidism is caused by hyperplasia in 7.3% which is relatively lower than western reports. Most of the PHPT cases can be managed by unilateral neck exploration guided by preoperative localization studies, and recently the MIP might become the standard operation in the near future.

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