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Original Article

Clinical and surgical approach to parathyroid adenomas: A single-center experience

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Abstract

Aim: Primary hyperparathyroidism is a clinical condition caused by excessive parathyroid secretion of the parathyroid glands and related hypercalsemia. Hyperparathyroidism is a common cause of hypercalcemia. In this study, we aimed to present the results of patients operated on due to parathyroidadenoma in our clinic.
Material and Methods: IPatients who underwent surgery for parathyroid adenoma in our clinic between January 2007 and January 2019 were included in the study. Clinical characteristics, biochemical data, treatment methods and results of the patients were analyzed retrospectively.
Results: 156 patients with a mean age of 50.8 years participated in the study. Female sex was 76.2%. Preoperative calcium level was found as 11.2+1.02 mg/dl, Parathormone level was found as 114.7+109.5 pg / ml. The most common clinical presentation was asymptomatic hypercalcemia (48.7%). While 89.7% of the patients had only parathoridectomy, 3.2% had total thyroidectomy and 7.1% had lobectomy due to associated thyroid pathology (10.3%). Intraoperative rapid parathormone was used in 54.4% of the patients. Frozen examination was performed in all patients. The most common localization was inferior left 39.7%. The most common ectopic localization was intratymic at 2.6%. The mean duration of postoperative hospital stay was 3.81+2.69 days. Three patients (1.9%) had persistent hyperparathyroidism and 6 patients (3.8%) had recurrent hyperparathyroidism. The mean follow-up was 57.2+39.5 months.
Conclusion: Proper preoperative evaluation, careful exploration, frozen examination and rapid parathormone test increase the success of parathyroid adenoma surgery.

Keywords: Primary hyperparathyroidism; parathyroidectomy: hypercalcaemia.

INTRODUCTION

TPrimary hyperparathyroidism (PHPT) is a disease characterized by hypercalcemia, hypophosphatemia and excessive bone resorption as a result of excessive parathormone release from the parathyroid gland (1). PHPT is the third most common endocrine disease after diabetes mellitus and thyroid diseases and its prevalence is increasing (2,3). The current prevalence of PHPT is between 0.25% and 0.66% of the population. It is seen 3 times more commonly in women when compared to men (1).

Most of the cases are sporadic and approximately 5% are familial. Reasons include single parathyroid adenoma in 80-85% of cases, double adenoma in 4-5%, 10-15% of multiple gland hyperplasia and parathyroid cancer in less than 1% (4). In the modern era, PHPT is usually detected incidentally during routine biochemical tests, and in this milder form, it is often asymptomatic, unlike the more severe PHPT associated with classical bone, renal, and neuropsychiatric manifestations (5). The basis of treatment, and the only definitive treatment, for PHPT is surgical resection of adenomatosis or hyperplastic parathyroid glands (6). First parathyroid surgery in history was a case involving bilateral neck exploration performed by Felix Mandl in 1925. Today, minimally invasive and

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robotic approaches are prominent in parathyroid surgery (7,8).

In this study, we aimed to present the results of patients who were surgically treated in our clinic with the diagnosis of parathyroid adenoma in the last 13 years, in the light of the literature.

MATERIAL and METHODS

Patients who underwent surgery with the diagnosis of parathyroid adenoma between January 2007 and January 2019 in the General Surgery clinic of Cukurova University were included in the study. Our indications for operation were patients with symptomatic PHPT and asymptomatic patients who met any of the Guideline criteria published in 2008, 2014 and 2016 (9-11). (Permission was obtained from the Ethics Committee on 08.03.2019 with the permission numbered 86/44). Patients under 18 years of age, secondary and tertiary hyperparathyroidism patients, patients with multiple endocrine neoplasia and patients whose medical records could not be reached were excluded. A common database was created by examining patient files, anesthesia records and hospital information system records. Using this database, patient information was evaluated retrospectively. Follow-up data were supported by telephone interviews with patients. Age, sex, presentation complaints, radiological imaging method used, Preoperative Ca (mg/dl), P (g/dl), PTH (pg/ml), ALP (U/L), Creatinine (mg/dL), Vitamin D level (g/mL) were evaluated. Normal ranges of biochemical parameters are 8.9-10.3 mg/dL for serum calcium, 2.4 to 4.7 mg/dL for serum phosphate, 38-126 U/L for alkaline phosphatase, 0.4 to 1 mg/dL for serum creatinine and 12 to 69 pg/mL for plasma intact PTH concentration and >30 ng/mL for vitamin D.

Imaging methods used for determining the localization of parathyroid pathology, surgical procedures, whether concurrent thyroid surgery was performed, intraoperative rapid parathormone use, postoperative complications, postoperative hospital stay, persistent or recurrent hyperparathyroidism during follow-up and mean follow-up were recorded. Neck ultrasonography (USG) and MIBI scintigraphy were performed before the operation to try and determing the localization of pathological parathyroid glands. All operations were performed under general anesthesia, head in extension, some with Kocher's necklace incision and some with a minimally invasive procedure. The patients who had Kocher's incision underwent unilateral neck surgery according to the localization studies. If the pathological gland could not be detected on the first surgical side, or in patients with negative USG and MIBI scintigraphy, bilateral neck exploration was performed. The parathyroid gland with a pathology was removed in patients undergoing minimally invasive surgery. Frozen section was routinely used to identify the parathyroid tissue and to separate it from the non-parathyroid tissue with good accuracy. 1 hemovac (HV) drain was inserted into the parathyroidectomy site according to the hemostasis status of peroperative patients and it was removed on the 1st or 2nd postoperative day. Miami criterion was used as the criterion for rapid parathormone evaluation. Compared to the highest basal value before excision, the criterion was the PTH level at the 10th minute after excision being below 50% (12).

Recurrent HPTH is defined as the patient having normal calcium and PTH for at least 6 months after a successful operation, followed by recurrent hyperparathyroidism. Persistent HPTH is defined as non-normalization of postoperative calcium and PTH values. All patients were informed about the surgical options and written informed consent was obtained.

Data were analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean and standard deviation (median and minimum-maximum where necessary).

RESULTS

156 patients with a mean age of 50.8 were included in the study. Female sex was dominant (76.2%). The mean preoperative calcium level was 11.2+1.02 and the preoparative parathormone level was 114.7+109.5. Most commonly, ultrasound and scintigraphic examinations were performed together for preoperative localization of adenomas (48.7%). Demographic data and the preoperative laboratory values of the patients are shown in Table 1.

The most common clinical presentation in patients was asymptomatic hypercalcemia (48.7%). Clinical presentations of the patients are shown in Table 2. While 89.7% of the patients only underwent parathyroidectomy, due to 10.3% having associated thyroid patholody, 3.2% had total thyroidectomy and 7.1% lobectomy. Histopathological examination of thyroid glands of the patients who underwent total thyroidectomy revealed thyroid papillary cancer in 2 patients, thyroid folicular cancer in 1 patient, and nodular colloidal hyperplasia in 13 patients. The most common parathyroid adenoma was seen in the inferior left area (39.7%). Four patients had intratymic, three patients had mediastanal, three patients had esophagialsulcus and one patient had intrathyroidal localization. Intraoperative rapid parathormone was used in 54.4% of the patients. Temporary hypocalcemia was observed in 9.6% of the patients, while no permanent hypocalcemia was seen in any patient. The mean duration of postoperative hospital stay was 3.81+2.69 days. Persistent hyperparathyroidism was seen in three patients (1.9%), and recurrent hyperparathyroidism was observed in 6 patients (3.8%). Five of the patients with recurrent hyperparathyroidism had double adenoma. These patients were reoperated and Parathormone level decreased to normal range during follow-up. The other patient with recurrent hyperparathyroidism was followed up medically. Double adenoma was detected in patients

with persistent hyperparathyroidism. Two patients were reoperated and parathormone levels decreased to normal range. The other patient did not accept the operation. These patients were operated in our clinic before the Intraoperative rapid parathormone measurement test was used.The mean follow-up period was 57.2+39.5 months. Surgical morbidity and clinical results of the operations performed are shown in Table 3.

Table 1. Preoperative characteristics of patients with primary hyperparathyroidism (PHPT)

Variables	
Age, mean ± SD (min-max)	50.8+13.3(19-85)
Sex, No (%)	
Female	119 (76.2)
Male	37 (23.8)
Preoperative laboratory parameters, mean ± SD (min-max)	
Serum Calcium (mg/dl)	11.2+1.02(7.8-15.6)
Serum Phosphate (mg/dl)	2.75+0.76(1.42-5.65)
Serum ALP (U/L)	223.4+166(66.9-1458)
Serum iPTH (pg/ml)	114.7+109.5(33-814)
Serum 25-OHD (ng/ml)	16.5+11.5(3.37-64)
Serum Creatinin mg / dL	0.72+0.28(0.25-2.84)
Imaging method used for preoperative localization, No. (%)	
Ultrasound	29.(18.6)
Scintigraphy	51.(32.7)
Ultrasound and scintigraphy	76.(48.7)

ALP: Alkaline phosphatase, 25-OHD: 25-hydroxyvitamin D, iPTH: Intact parathyroid hormone, SD: Standard deviation

Table 2. Clinical manifestations in patients

Symptoms	No. (%)
Asymptomatic hypercalcemia	76 (48.7)
Diffuse body pain	30 (19.2)
Swelling in neck	18 (11.5)
Urolithiasis	12 (7.7)
Back pain	8 (5.1)
Fatigue	6 (3.8)
Hypertension	4 (2.6)
Apathy and depression	1 (0.7)
Nausea and vomiting and fatigue	1 (0.7)

Table 3. Operative procedures, surgical morbidity, and clinical outcome

Surgical Approach	No. (%)
Parathyroidectomy	140 (89.7)
Parathyroidectomy + Lobectomy	11 (7.1)
Parathyroidectomy + Total thyroidectomy	5 (3.2)
Parathyroid adenoma localization	
Right (superior)	26 (16,7)
Right (inferior)	41 (26,3)
Left (superior)	16 (10,3)
Left (inferior)	62 (39,7)
Intrathymic	4 (2,6)
Mediastinal	3 (1,9)
Oesophagial sulcus	3 (1,9)
Intrathyroidal	1(0.6)
Intraoperative parathyroid hormone onitoring	85 (54.4)
Postoperative complication	
Transient hypocalcemia	15 (9.6)
Wound infection	1 (0.64)
Postoperative length of hospital stay (day) mean ± SD (min-max)	3.81+2.69(1-13)
Persistent Hyperparathyroidism	3 (1.9)
Recurrent Hyperparathyroidism	6 (3.8)
Followup period (month), mean ± SD (min-max)	57.2+39.5(6-149)

DISCUSSION

Primary hyperparathyroidism is the most common cause of hypercalcemia in patients treated as outpatients (13). In the literature, the annual incidence of PHPT worldwide has been reported to be 20 cases per 100,000 inhabitants and the prevalence of PHPT is between 0.5 and 2% (14-16). The majority of patients with PHPT have a single, benign, parathyroid adenoma. Parathyroid adenoma accounts for approximately 80% of PHPT cases. Multiglandular disease, in which quadruple parathyroid hyperplasia is the predominant form, occurs in 15-20% of cases. Multiglandular disease also manifests as two and, very rarely, three adenomas. Parathyroid carcinoma is less than 1% of all PHPT cases (14).

The highest incidence of PHPT is at the beginning of postmenopausal years, coinciding with loss of estrogen. It is 4 times more common in women than in men (17,18). Although the mean age was 50.8 in our series, the number of female patients were 3 times higher than men. Biochemical confirmation is required when PHPT is suspected or hypercalcemia is detected. The differential diagnosis of hypercalcemia is rather broad. The diagnosis of PHPT is confirmed by inappropriate intact PTH elevation associated with high serum calcium levels, excluding common causes of secondary HPT, such as renal failure, vitamin D deficiency, intestinal absorption abnormalities, and renal escape syndrome (1,19). Repeated measurements are necessary in primary hyperperparathyroiditis because patients may be intermittently normocalcemic, although they are often hypercalcemic.

There are three biochemical forms of PHPT. The classic form is the hypercalcemic form of PHPT, in which patients show increased serum calcium and PTH concentrations. In the second form, patients have hypercalcemia, but PTH levels are within normal reference ranges. In the third form, PTH levels were elevated but total and ionized serum calcium concentrations are normal, this is called "normocalcemic PHPT" (20). Therefore, when serum total calcium level is normal with an elevated PTH level, an ionized serum calcium is required to confirm the diagnosis. If ionized calcium is high, the patient has conventional PHPT. It is not considered eucalcemic or normocalcemic. As in the classical form of PHPT, it is unnecessary to obtain ionized serum calcium when the initial total calcium level rises. The latest guidelines are for the diagnosis of PHPT recommends the use of total Ca, not ionized Ca, since ionized Ca measurement is not widely available (21).

For patients with suspected normocalcemic PHPT, disorders that cause secondary hyperparathyroidism such as chronic kidney disease, vitamin D deficiency and gastrointestinal malabsorption problems such as short bowel syndrome, Crohn's disease, or previous Roux-en-Y bypass surgery should be excluded (20). When vitamin D deficiency occurs in patients with PHPT, they may initially be seen as normocalcemic, but after vitamin D supplementation they become hypercalcemic and switch to the classic PHPT form. However, since vitamin D deficiency is also a cause of increased PTH, when vitamin D replacement is performed in a non-PHPT patient with normal calcium levels, the PTH level may return to normal before hypercalcemia develops. There is also evidence that normocalcemic PHPT may be the first stage in a biphasic disorder progressing to hypercalcemic PHPT (6,20). It is recommended to measure 25 (OH) –vitamin D levels in all patients with PHPT. The recommended vitamin D levels are controversial. D vitamin threshold levels above 20-30 ng/ml are recommended (21,22). In our series, the mean calcium level was found to be 11.2 mg/dl and 25-OHD (ng/ml) at the time of admission was 16.5 ng/ml. Preoperative vitamin D replacement was performed in the patients who had vitamin D deficiency, to keep vitamin D levels at 20 ng/dl.

PTH levels in western studies were shown to be above 100 pg/mL and it was above 600 pg/mL in eastern series (23). In our series, our average PTH level was found to be 114.7, similar to the western series. Parathyroid adenomas rarely acquire very large dimensions and very high hypercalcemia causes serious complaints. Diagnosis is made as a result of the fact that hypercalcemia is noticed during routine examinations or people present with different symptoms in later stages (24).

The clinical presentation of parathyroid adenoma varies from asymptomatic disease to classical symptomatic disease with renal and/or skeletal complications. Patients with parathyroid adenoma used to present with clinical findings of prolonged disease such as nephrolithiasis, osteitis fibrosa cystica, Brown tumors, band keratopathy, bone pain, abdominal gurgling, psychological complaints, excessive fatigue, myopathy and muscle atrophy (1,4,25). Over the past 40 years, the presentation of PHPT has changed. Today, most patients do not have the classic symptoms or signs associated with PHPT at the time of diagnosis and are often detected by incidental findings. Asymptomatic PHPT has been the dominant phenotype of PHPT in modern western populations with a prevalence of 72.7% to 95% (26,27). In western societies, one-third of the presenting symptoms are renal symptoms, whereas the proportion of patients with bone disease has gradually decreased in the last 50 years to 5-10% (28). In our series, 48.7% of patients presented with asymptomatic hypercalcemia, 19.2% with generalized body pain, 11.2% with swelling in the neck, and 7.7% with urolithiasis. When the patients were evaluated appropriately, we found that nonspecific symptoms such as diffuse body pain and fatigue were present in many patients who were considered asymptomatic.

New imaging and diagnostic methods for localizing the pathological lesion of PHPT have led to a change in the surgical approach of PHPT and the ability to safely perform surgical treatment (23). USG and parathyroid scintigraphy are the most common imaging modalities, but computed tomography and magnetic resonance imaging can

also be used. USG is one of the most common imaging modalities for the neck. Its sensitivity in the detection of parathyroid adenoma varies between 72-89% (29). Tecnesium99-m labeled 2-methoxyisobutyl-isonitrile scintigraphy as parathyroid scintigraphy is superior to other scintigraphy methods because of its short half-life, better image quality and lower radiation risk (30). Scintigraphy is the gold standard for the detection of preoperative localization of hyperfunctioning parathyroid tissue. Thin-section contrast-enhanced CT can be used to localize the parathyroid adenoma. The advantage of CT over USG is the detection of ectopic adenomas, especially in the mediastinum. Combination of imaging methods in parathyroid pathologies will increase the accuracy of localization.

In patients with a solitary adenoma proven by PHPT, the sensitivity rate has been reported as 95% when preoperative USG and scintigraphy were combined, 80% when USG is used alone, and 87% when scintigraphy is used alone(31). We prefer to use ultrasound combined with parathyroid scintigraphy in our patients. We used Single Photon Emission Computed Tomography (SPECT) in patients whose localization could not be detected.

While the main surgical indication in the 1970s was kidney stones, in our era the indications for surgical treatment in symptomatic patients are; hypercalcemia, pronounced hypercalciuria, 30% reduction in creatinine clearance, lumbar vertebrae, hip or distal radius bone density decrease, the patient being younger than 50 years, patients who don't accept medical treatment or those who are unsuitable for medical treatment (9-11). Surgery should be recommended in asymptomatic patients if there is no obstacle to surgery, because dealing with the complications of hypercalcemia is difficult.

The type of surgical intervention performed during surgery has also changed over the years. Rather than bilateral neck exploration, which has been accepted as the gold standard, the rate of minimally invasive surgical procedures is increasing day by day. However, minimally invasive procedures depend on the precise preoperative localization of parathyroid tissue. Bilateral exploration of the parathyroid glands increases the success of surgical treatment in patients with asymmetric parathyroid hyperplasia or double parathyroid adenoma. Unilateral exploration can be performed in patients whose diagnosis of unilateral parathyroid adenoma is confirmed by preoperative and intraoperative imaging methods and assisting techniques, but bilateral exploration is safer in suspected patients (32).

In our series, 89.7% of the patients underwent only parathyroidectomy, while 10.3% underwent thyroidectomy due to associated thyroid pathology. The incidence of concomitant thyroid nodules in patients presenting with PHPT ranges from 20 to 60%, whereas in patients presenting with thyroid disease, PHPT is reported to be much lower, between 0.3% and 1% (33). Thyroid nodules or thyroid cancer may be overlooked during index operation when the surgical management of PHPT is performed with a focused, unilateral approach. Therefore, all patients with PHPT should undergo preoperative ultrasonography to localize parathyroid adenomas and to detect associated thyroid nodules. If thyroid nodules are detected, thyroid fine needle cytology should be performed and appropriate thyroid resection should be performed during parathyroidectomy. Alternatively, preoperative evaluation of serum PTH and calcium concentrations in patients with thyroid disease is recommended to address both diseases simultaneously (33).

In our series, all patients were evaluated for thyroid nodules. In our series, in the patients who underwent thyroidectomy, 2 patients had thyroid papillary cancer,1 patient had thyroid folicular cancer and 13 patients had nodular colloidal hyperplasia. Generally, the superior glands are smaller than the inferior glands. Surgical exploration may also be more difficult, as the inferior parathyroid glands may be located in a larger area than the superior parathyroid glands. Although there are few variations, there are usually 4 parathyroid glands in humans. Two of the glands are usually located on the bottom and the other two on the top. Parathyroid adenomas usually develop from the lower glands (32). Very rarely, parathyroid glands may be intrathyroidally localized. Intrathyroidal placement of parathyroids is 0.2-3% in autopsy series (34). Rossi and Cady reported that the actual intrathyroid parathyroid rate was below 2% (35). In a study of persistent and recurrent cases, Shen et al. found ectopic gland localization as paraesophageal (28%), mediastinal (26%), intratymic (24%), intrathyroid (11%), and carotid sheath (9%) (36). In our series, adenomas were most commonly originating from the inferior parathyroid glands. In addition, ectopic localization was intrathymic in four patients, mediastinal in three patients, esophageal sulcus in three patients, and intrathyroidal in one patient.

It is also possible to evaluate whether there is a pathology of the parathyroid glands found during surgical exploration with frozen section in pathology, in addition to the macroscopic evaluation by the surgeon. The risk of persistent hypoparathyroidism is high in such interventions, because excisional biopsies from normal glands may damage the intact glands. Therefore, it is more appropriate for surgeons with sufficient experience to decide whether the glands are pathological or normal with their macroscopic evaluation. Frozen examination can be performed if there is any doubt about whether the removed specimen is a parathyroid gland. We used frozen section for every patient in our series.

With the aid of intraoperative measurement of PTH levels during parathyroidectomy, the surgeon can be sure that all hyperfunctional parathyroid glands are removed. PTH is produced only in the parathyroid glands and the intact PTH has a half-life of <5 minutes. Therefore, blood concentrations of PTH will rapidly decrease shortly after removal of all overexpressing parathyroid tissues (37). Previous studies have shown that IOPTH levels can be

used to predict surgical treatment. Alhefdhi et al. showed that PTH levels decreased by 50% in 96.5% of patients, and 36% of these patients had multiple glands resected and 100% of the patients were cured (38). Intraoperative rapid parathormone measurement has been used in our clinic since 2012 and we used it in 54.4% of our patients.

Hypocalcemia is the most common complication both after thyroid surgery and after parathyroid surgery, and the most commonly accused condition is hungry-bone syndrome. In large parathyroidectomy series, this syndrome has been reported to develop in up to 13% of the patients postoperatively (23). Other common complications are the continuation of the disease due to not being able to find the diseased gland, laryngeal nerve damage, bleeding and infection (39).

In our study, transient hypocalcemia developed in 9.6% of the patients. Complaints of the patients improved with appropriate calcium replacement therapy; hypocalcemia was not persistent in any patient. None of our patients developed laryngeal nerve damage. One patient developed wound infection. Our duration of postoperative hospital stay was 3.8 days. The most important factor prolonging postoperative hospital stay was the increased hospitalization period of patients with hypocalcemia. Even if performed by specialist endocrine surgeons, the success rate of PHPT is not 100%, and the recurrent or permanent PHP rate is reported to be 3-5% (40). In our series, recurrent hyperparathyroidism was seen in 3.8% of the patients and persistent hyperparathyroidism was seen in 1.9%. The mean follow-up period was 57.2 months.

The most important limitation of our study was its retrospective nature. In addition, only patients who underwent surgery for parathyroid adenoma were included in the study; however, our patient population was as large as the series in the literature. We believe that our study provides comprehensive data on surgical treatment and clinical features of parathyroid adenomas and contributes to valuable reference data.

CONCLUSION

We believe that surgery will continue to be an indispensable treatment modality even in asymptomatic patients due to long-term complications in primary parathyroid adenoma. Surgical treatment of parathyroid adenomas is a safe surgical procedure with a high success rate and low complication rate with the help of appropriate preoperative evaluation and localization studies.

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