

SURGICAL TREATMENT OF PRIMARY HYPERPARATHYROIDISM

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Abstract

Background: With the use of routine calcium evaluation, the incidence of primary hyperparathyroidism (pHPT) has considerably increased. The aim of our study was the assessment of the morbidity and the outcome of surgically treated patients with pHPT.

Methods: The charts of 279 patients (204 female, 75 male, median age: 58 years) who underwent surgery for pHPT between 1989 and 1999 were retrospectively reviewed. A follow-up was carried out on 235 patients after a mean period of 3.6 years (0.2 – 10 years).

Results: In 148 patients a unilateral, and in 130 patients a bilateral approach was taken. Transplanted parathyroid tissue was removed from the left forearm of one patient. At follow-up persistent hypocalcemia was seen in 30 patients (20 after bilateral, 10 after unilateral exploration). 6 patients (1 after bilateral, 5 after unilateral exploration) revealed a newly developed persistent paresis of the recurrent laryngeal nerve. In 5 patients persistent (1 after unilateral, 4 after bilateral exploration) and in 5 patients recurrent (2 after unilateral, 3 after bilateral exploration) pHPT could be observed.

Conclusion: Both unilateral and bilateral cervical exploration for pHPT have a high rate of success with a low morbidity. Therefore, patients with assumed asymptomatic pHPT with unspecific neuropsychological abnormalities should also be evaluated for surgical intervention.

Key words: primary hyperparathyroidism, surgery, outcome, unilateral exploration, bilateral exploration

INTRODUCTION

Some decades ago primary hyperparathyroidism (pHPT) was thought to be a rare disease, mostly affecting the bones and the kidneys. With the use of standard laboratory calcium determination many patients are detected incidentally due to hypercalcemia, which has led to a considerable increase in the frequency of pHPT. The incidence is reported to be approximately 100 – 200 patients / 100 000 inhabitants making pHPT one of the most frequent forms of endocrine diseases, next to diabetes mellitus and thyroid diseases (Heath et al. 1980, Funke et al. 1997, Wermers et al. 1997). Additionally, the clinical picture of the disease has changed. The correct diagnosis can be made much earlier before the classical symptoms such as “kidney stones, painful bones, abdominal groans, psy-

chic moans and fatigue overtones” have developed. Nowadays, many patients present asymptotically or with only mild and subtle symptoms such as irritability, fatigue, mood swings, forgetfulness, weakness and adynamic and depressive disbehaviour, which are often difficult for the primary physician to recognise. Whereas symptomatic pHPT is a clear indication for surgical therapy to relieve the symptoms, the therapeutic consequences in the case of patients with asymptomatic disease or only subtle symptoms are still controversial. In addition, in the case of cervical exploration the surgical approach with respect to bilateral or scan-directed unilateral parathyroidectomy is under debate. The aim of our study was the assessment of the morbidity, the mortality and the long-term follow-up of surgically treated asymptomatic and symptomatic patients with pHPT with respect to the surgical approach.

MATERIAL AND METHODS

The clinical charts of 279 patients who underwent surgery for pHPT at our institution between 01.01.1989 and 31.12.1999 were reviewed with regard to the preoperative symptoms, the endocrinologic evaluation, the imaging procedures, the surgical procedures, the morbidity and mortality and the pathologic findings. The preoperative diagnostic work-up included the evaluation of the concentration of calcium, of intact parathormone or parathormone and of phosphate. The patients were either classified as symptomatic or asymptomatic. The diagnosis of symptomatic pHPT was made by means of an evaluation of the typical symptoms and the biochemical abnormalities, including an elevated calcium concentration in combination with elevated parathormone or intact parathormone concentration, and a decreased concentration of phosphate. Asymptomatic was defined as a patient presenting without the typical symptoms for pHPT but with biochemical abnormalities. From 1991 onwards, the patients presenting with asymptomatic pHPT were treated surgically in accordance with the guidelines established by the National Institutes of Health Consensus Development Conference (Consensus Development Conference Panel 1991). All patients had been evaluated preoperatively for the function of the vocal cord. The surgical approach with respect to a unilateral or a bilateral parathyroidectomy was carried out on the basis of the results of the preoperative em-

ployed imaging modalities and in the case of former cervical thyroid or parathyroid resections. A unilateral approach was taken if a unilateral disease was clearly revealed by imaging methods. The detected parathyroid gland was identified intraoperatively and resected without examination of the contralateral gland. The diagnosis was confirmed by intraoperative and postoperative histopathological examination of the surgical specimen and a biopsy of the ipsilateral hypoplastic gland. A bilateral approach was taken in the case of suspected hyperplasia of more than one gland, in the case of MEN I or in the case of unclear imaging results. By means of this approach, all four glands were identified intraoperatively, the enlarged gland or glands were resected, and the diagnosis was also confirmed by intraoperative and postoperative histopathological examination of resected specimen and a biopsy of the remaining glands. Postoperatively, before discharge from hospital, all patients were re-examined with respect to the function of the laryngeal nerve by means of laryngoscopy and measurement of the calcium concentration. A follow-up could be carried out on 235 patients. The patients were re-examined in our endocrinologic outpatient clinic, or by using a standardised questionnaire sent to the primary physician with the evaluation of the biochemical parameters, the current complaints, a paresis of the recurrent laryngeal nerve and relapse or persistence of pHPT.

RESULTS

Of the 279 patients operated for pHPT, 204 patients were female and 75 patients were male with a relation of 2.7 : 1 and a median age of 58 years. In the case of 165 patients when they presented with the typical symptoms for pHPT, the diagnosis was made clinically and was confirmed biochemically (Fig. 1).

In 83 patients the diagnosis was made incidentally when a hypercalcemia was discovered during routine calcium evaluation for other reasons. 17 patients presented with persistent, and 14 patients with recurrent disease after prior cervical exploration.

Comparing the portion of asymptomatic patients to all patients operated for pHPT between 1989 and 1999, it came to an increase of up to 53 % in the last year of this series (Fig. 2).

Biochemical evaluation revealed an elevated calcium concentration of median 2.95 mmol/l in 210 patients. The intact parathormone with a median concentration

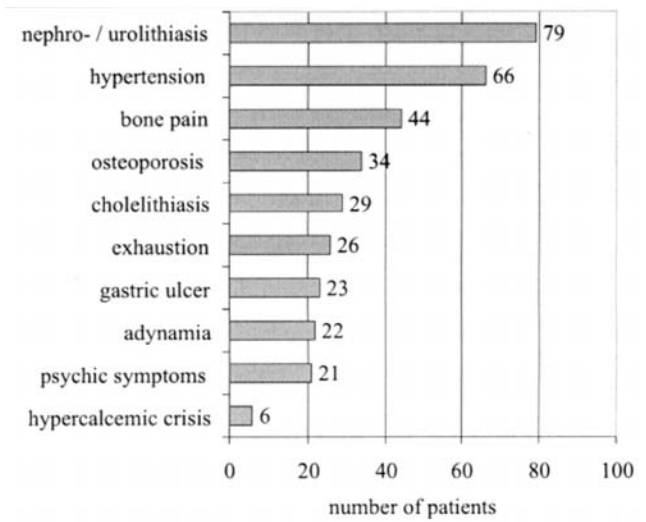


Fig. 1. Symptoms of the 165 patients with symptomatic primary hyperparathyroidism (repeated counting possible).

of 144 pg/ml was elevated in 195 patients and the parathormone was elevated in 59 patients with a median concentration of 439 pg/ml.

Cervical ultrasound (US) was the most frequently employed method used in all patients, cervical computed tomography (CT) in 50 patients, sestamibi scintigraphy (Mibi) in 30 patients, technetium subtraction scintigraphy (TE/TH) in 28 patients, selective catheterization of the cervical veins with measurement of the parathormone concentration in 22 patients and cervical magnet resonance imaging in 14 patients.

The surgical approach taken was a cervical exploration in 266 patients, a sternotomy in 7 patients and a cervical exploration with sternotomy in 2 patients. Transplanted parathyroid tissue was removed from the left forearm of one patient. In the case of 148 patients a unilateral exploration was performed, and a bilateral on 130 patients. In 73 patients the unilateral approach was taken on the right side, in 75 patients on the left. The diagnosis of MEN I was established preoperatively in 13 patients. An ectopic localisation of the parathyroid tissue was revealed in 13 patients. Postoperative bleeding occurred in 10 patients after bilateral and in 10 patients after unilateral exploration. 7 of these patients required a second operation to stop the bleeding. There was one fatality in the early postopera-

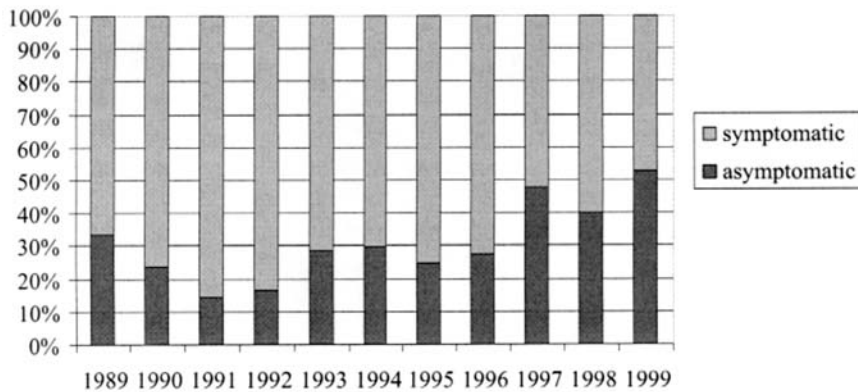


Fig. 2. Proportion of asymptomatic patients in relation to all patients operated between 1989 and 1999.

tive course. This 69-year old patient had died due to heart failure after bilateral exploration for a unilateral adenoma.

Postoperative histopathological examination revealed a unilateral adenoma in 235 patients, a double adenoma in 2 patients, a hyperplasia of 2 glands in 9, of 3 glands in 7, of four glands in 12 patients and a carcinoma in 1 patient. In 6 patients no adenoma or other reason for pHPT could be found, no data regarding the histopathological results could be evaluated in 7 patients.

Postoperatively, before discharge from hospital, newly developed unilateral paresis of the recurrent laryngeal nerve occurred in 19 patients. 11 of these patients had been operated using a bilateral approach and 8 from a unilateral approach. Of these 19 patients, 6 had previous parathyroidectomies, 2 had former thyroidectomies, and in 6 patients a hemi-thyroidectomy or a subtotal thyroidectomy was carried out simultaneously. In one patient the recurrent laryngeal nerve was resected due to carcinoma of the parathyroid gland.

After a mean period of 3.6 years (0.2 – 10 years) it was possible to carry out a follow-up on 235 patients. 33 patients had died during the follow-up. A persistent hypocalcemia with substitution of calcium was seen in 20 patients after bilateral, and in 10 patients after unilateral exploration. In 10 of these 30 patients a subtotal, and in 2 patients a total parathyroidectomy had been carried out. During the follow-up 1 patient presented with persistent paresis of the recurrent laryngeal nerve after a unilateral, and 5 patients after a bilateral approach. The recurrent laryngeal nerve of one of these patients was resected due to parathyroid carcinoma, 4 patients had undergone former cervical operations due to persistent or recurrent pHPT, and one patient had undergone simultaneous subtotal thyroidectomy. At the follow-up persistent pHPT was observed in 5 patients and recurrent pHPT in 5 patients. After bilateral exploration, 4 persistent and 3 recurrent pHPT were observed, and 1 persistent and 2 recurrent pHPT could be seen after unilateral exploration. Of the 83 asymptomatic patients, 9 were hypocalcemic at the follow-up, none of the asymptomatic patients had permanent vocal cord paralysis, whereas 3 patients suffered from recurrent pHPT.

DISCUSSION

Primarily because of the lack of highly accurate preoperative localising studies, the standard operation for pHPT has consisted of a bilateral neck exploration with the examination of all four parathyroid glands, the detection of abnormal located parathyroid tissue and resection of the pathologic tissue without preoperative cervical imaging (Norman et al. 1998). With the corresponding experience of the surgeon in approximately 95 - 99 % of the patients with bilateral cervical exploration, the operation can be carried out successfully, comparable to the success rate of 95 % found in our series (Russell and Edis 1982, van Heerden and Grant 1991, Uden et al. 1992, Funke et al. 1997, Delbridge et al. 1998, Low and Katz 1998, Walgenbach et al. 2000, Bergenfelz et al. 2002, Schell et al. 2003). Due to the high percentage of adenomas as the

unilateral source of the excessive production of parathormone, with a frequency of up to 80 – 90 % - as it can be seen in our series - some authors favour the unilateral approach with preceding imaging of the parathyroid glands (Funke et al. 1997, Low et al. 1998, Vogel et al. 1998, Schell et al. 2003). Also, with the use of a unilateral scan-directed approach, a high cure rate comparable to the bilateral approach can be achieved (Russell et al. 1990, Tibblin et al. 1991, Robertson et al. 1996, Kountakis et al. 1999, Bergenfelz et al. 2002, Udelsman 2002, Schell et al. 2003, Sidhu et al. 2003). In our series, compared to the bilateral approach, the unilateral approach was even slightly better with a cure rate of 98 %. In a prospective randomised controlled trial comparing the unilateral and the bilateral exploration, Bergenfelz et al. could show that patients undergoing a unilateral procedure had a lower incidence of biochemical and severe symptomatic hypocalcemia in the early postoperative period, compared with patients undergoing bilateral exploration (Bergenfelz et al. 2002). They concluded that unilateral neck exploration with intraoperative histopathological examination is a valid surgical strategy with distinct advantages, especially for patients with solitary parathyroid adenoma. Tibblin et al. was able to reveal that the rate of postoperative permanent hypocalcemia increases if a bilateral exploration with identification of all 4 parathyroid glands has been carried out (Tibblin et al. 1991). We could also show a lower rate of postoperative vocal cord paresis in patients treated by a unilateral scan-directed exploration. Also, compared to the bilateral approach, other authors have found a reduced morbidity, reduced complication rate, a better cosmetic outcome, a reduction of injury of the recurrent laryngeal nerve, and shorter operation times and stay at the hospital, leading to lower costs (Lucas 1990 et al., Worsey et al. 1993, Robertson et al. 1996, Norman et al. 1998, Vogel et al. 1998, Reeve et al. 2000). One major reason for increased morbidity including the development of permanent paresis is former cervical exploration for parathyroidectomy. In 4 of the 6 patients with permanent paresis, previous parathyroid explorations had been carried out. The amount of scar and distortion of tissue planes caused by the initial neck exploration makes re-operation much more difficult, with the recurrent laryngeal nerve being difficult to identify, thus leading to higher morbidity (Willeke et al. 1997). These patients should only be re-operated in specialised centers by experienced surgeons.

One presupposition for the unilateral approach is the clear and correct localisation of the abnormal parathyroid tissue. Duh et al. devised a mathematical model that predicts the rate of failure of unilateral exploration for pHPT (Duh et al. 1992). Assuming a rate of single unilateral adenoma of 80 % and an accuracy of 60 % for localising investigations and a 5 % probability of not finding an abnormal gland, this model predicts a 4.97 % failure rate for unilateral exploration. However, the accuracy of imaging methods for the detection of pathologic parathyroid tissue has increased in the past years, leading to a greatly lower failure rate. Some authors favour the bilateral exploration because preoperative localizing techniques are more expensive than a non-directed bilateral neck exploration in the

initial treatment. Fahy et al. proved that the use of any localizing strategy reduces the total charges from immediate hospital discharge, risk of persistent pHPT and cumulative risk of recurrent laryngeal nerve injury, in comparison to non-directed bilateral exploration (Fahy et al. 2002). This can be seen in our series where patients were discharged 2 days earlier from hospital after unilateral cervical exploration. Claims that scan-directed parathyroid operation is the cheapest, fastest, and most successful means of treatment were not supported by the data from Schell (Schell et al. 2003). Schell et al. demonstrated operative times and treatment outcomes using the bilateral approach with costs that are approximately one-third less than those for scan-directed, minimally invasive operation for pHPT. However, the cost of the preoperative localization is highly dependent on the imaging method and the amount of studies used. We favour cervical ultrasound as a cheap imaging method that can be performed with an accuracy of up to 90 % by experienced radiologists (Lucas et al. 1990, Vogel et al. 1998).

Since the advent of routine calcium screening 3 decades ago the clinical spectrum of pHPT has changed on the one hand and the incidence has increased on the other, leading to a strong increase of parathyroidectomies (Delbridge 1998). There is a clear indication for surgical therapy in symptomatic patients, in asymptomatic patients the correct therapy is still a matter of debate: Both a conservative therapy with close follow-up and a surgical therapy is recommended. In 1990, National Institutes of Health Consensus Development Conference established guidelines regarding the criteria for the close follow-up or surgical approach in asymptomatic patients, which were modified in 2002 (Consensus Development Conference Panel 1991, Bilezikian et al. 2002). Apart from the 6 recommendations, the guidelines from 2002 considered neuropsychological abnormalities which included weakness and fatigue, depression, intellectual weariness and increased sleep requirements with a negative influence on the quality of life that influence the decision-making process of the correct therapeutic approach (Bilezikian et al. 2002). At this time it is not possible to predict preoperatively which patients will benefit from surgical therapy, as their symptoms may become apparent only after parathyroidectomy, with most of the patients experiencing subjective improvement after a successful parathyroidectomy. When these patients with assumed asymptomatic pHPT are examined thoroughly enough, only few patients, with a prevalence of approximately 5 - 10 %, are actually totally asymptomatic or without associated conditions (Chan et al. 1995, Hasse et al. 2000, Walgenbach et al. 2000, Eigelberger et al. 2004). Eigelberger et al. compared patients with asymptomatic pHPT who met or failed the criteria and recommendations before and after parathyroidectomy (Eigelberger et al. 2004). They were able to reveal that there was no difference in the symptoms between those patients with pHPT who met the criteria for parathyroidectomy and those who did not. Furthermore, they found that patients in both groups benefited symptomatically after successful parathyroidectomy. They concluded that virtually all patients with pHPT benefit symptomatically, metaboli-

cally, and from a survival point of view after successful parathyroidectomy, so that most patients with pHPT should be treated surgically by an experienced surgeon. Therefore, due to the high cure rate and low morbidity found in our series - independent from the surgical approach - we also support a liberal policy with respect to cervical exploration, especially in the case of asymptomatic or assumed asymptomatic patients with pHPT. Hedback et al. revealed that early surgery decreases the risk of premature death in mild cases of the disease (Hedback et al. 1991). Walgenbach et al. demonstrated a mortality significantly higher than the expected mortality risk for the German population as a whole during follow-up, and they emphasise the importance of early diagnosis and early surgical treatment for pHPT, even in the absence of manifest symptoms (Walgenbach et al. 2000).

In conclusion, unilateral or bilateral cervical exploration for pHPT is connected with a high success rate and a low morbidity. Only cervical re-operation increases the morbidity. Therefore, patients with assumed asymptomatic pHPT with unspecific neuropsychological abnormalities should also be evaluated for surgical intervention. Because of the better outcome with respect to morbidity for patients with unilateral exploration without deterioration of the success rate, we favour the unilateral approach with the preoperative use of imaging methods, including cervical ultrasound, as a cheap localisation procedure with a high rate of accuracy in experienced hands.

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