ORIGINAL ARTICLE

The Outcome of Subtotal Parathyroidectomy for the Treatment of Hyperparathyroidism in Multiple Endocrine Neoplasia Type 1

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Background: The efficacy of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1 (MEN 1) is unclear. The long-term outcome and optimal timing of operation remain controversial.

Objective: To determine the long-term outcome of parathyroidectomy for primary hyperparathyroidism in the presence of MEN 1.

Design: Case series and retrospective analysis.

Setting: Tertiary referral center.

Patients: Patients with MEN 1 from 2 families.

Interventions: Subtotal parathyroidectomy, ie, resection of 3½ parathyroid glands from each patient.

Main Outcome Measures: Recurrence of hyperparathyroidism.

Results: Thirty-seven patients underwent subtotal parathyroidectomy. Overall, persistent postoperative hypoparathyroidism developed in 24%, normocalcemia was maintained in 46%, and hyperparathyroidism recurred in 30%. However, after adjustment for the duration of follow-up (by using the Kaplan-Meier method), the cumulative recurrence rates for hyperparathyroidism were 15% at 2 years, 23% at 4 years, 55% at 8 years, and 67% after 8 years. Early recurrence of hyperparathyroidism (within 5 years of operation) was less likely to develop in patients in whom ionized calcium levels of 1.00 mmol/L (4.00 mg/dL) or less were achieved during the perioperative period than in patients in whom this degree of hypocalcemia failed to develop (P=.01).

Conclusions: While relatively long periods of disease remission are possible after subtotal parathyroidectomy, our results indicate that recurrent hyperparathyroidism eventually develops in most patients with MEN 1.

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THE ROLE of parathyroidectomy in the management of sporadic primary hyperparathyroidism (PHPT) is well established. The cure rate exceeds 90%.[1] Persistent and recurrent PHPT after operation usually occurs in the presence of multiple gland parathyroid disease, multiple adenomas, or diffuse hyperplasia of the parathyroid glands.[2,3] Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant condition typified by hyperplasia of the parathyroid glands, gastroenteropancreatic neuroendocrine neoplasia, and pituitary neoplasia.[4-6] Primary hyperparathyroidism is the most prevalent abnormality in MEN 1, occurring in virtually all persons who inherit the underlying gene defect.[6] Hypercalcemia is often the first manifestation of MEN 1; biochemical disease usually becomes detectable during the second or third decade of life. The optimal timing and type of parathyroidectomy for patients with MEN 1, however, remain controversial.

Some authors have described the efficacy of subtotal parathyroidectomy (resection of 3-3½ parathyroid glands) for the treatment of hyperparathyroidism in MEN 1.[7,8] Long-term recurrence rates less than 20% are reported.[7,8] Moreover, successful resolution of hyperparathyroidism after removal of only 1 or 2 enlarged parathyroid glands has also been described.[9] However, other reports highlight a high rate of disease recurrence despite subtotal resection of the parathyroid glands.[1,10]

Possible explanations for disparity between the findings of these studies are the inclusion of patients with sporadic hyperparathyroidism and an insufficient period of follow-up in those studies describing a good response to parathyroidectomy.[1,11] The cumulative recurrence rate for hyperparathyroidism in the re-

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PATIENTS AND METHODS

Two MEN 1 kindreds have been identified in Tasmania.[13] The larger kindred includes more than 160 patients with MEN 1; 13 patients with MEN 1 have been detected in a smaller unrelated pedigree. We reviewed the outcome of subtotal resection of the parathyroid glands (residuum approximately half the size of 1 normal parathyroid gland) in 37 patients deriving from these 2 MEN 1 kindreds. In this study, 32 of 37 patients (86%) belonged to the larger kindred. In 28 of 37 (76%) of the cases, the operation was performed by 1 surgeon (J.J.S.).

Hypercalcemia was defined by an albumin-corrected calcium level greater than 2.55 mmol/L (10.20 mg/dL), an ionized calcium level (corrected to pH 7.4) greater than 1.29 mmol/L (5.16 mg/dL), or a total calcium level of greater than 2.75 mmol/L (11.00 mg/dL). Elevation of the serum calcium level was confirmed on 2 or more separate occasions. Persistent hyperparathyroidism and recurrent hyperparathyroidism were defined by postparathyroidectomy hyperparathyroidism occurring before and after the sixth postoperative month, respectively.

Hypoparathyroidism was defined by serum ionized or albumin-corrected calcium levels below 1.10 mmol/L (4.40 mg/dL) or 2.00 mmol/L (8.00 mg/dL), respectively, that persisted beyond the sixth postoperative month. The presence of pituitary and pancreatic disease was assessed by using radiological (computed tomography and magnetic resonance imaging), sonographic, and biochemical techniques. Numerical data are presented as the mean±SEM. When appropriate, the χ^2 and unpaired Student *t* test were used for the statistical analysis of data. Follow-up data were analyzed by using the Kaplan-Meier method.

port by O'Riordain et al[7] was 16.4% at 10 years; however, 41% of patients in this study did not have a history in the immediate family of MEN 1. Given the relatively high prevalence of sporadic endocrinopathy in the general population (eg, hyperparathyroidism, pituitary tumor, and adrenal adenoma), many patients with an MEN 1 phenotype in whom a confirmatory family history is absent may not carry the MEN 1 gene.[1,12] Furthermore, even in the presence of established familial MEN 1, cases of sporadic hyperparathyroidism may confound the interpretation of data. Teh et al[11] reported the occurrence of hyperparathyroidism in a MEN 1 family member who was not a gene carrier.

Thus despite extensive study, the efficacy of subtotal parathyroidectomy among patients with definite MEN 1 remains unclear. We report the results of subtotal parathyroidectomy in 37 patients deriving from 2 large MEN 1 kindreds.

RESULTS

The histopathologic characteristics of resected parathyroid tissue were consistent with hyperplasia of the parathyroid glands. Hyperparathyroidism persisted or recurred in 11 (30%) of 37 patients overall as shown in the following tabulation:

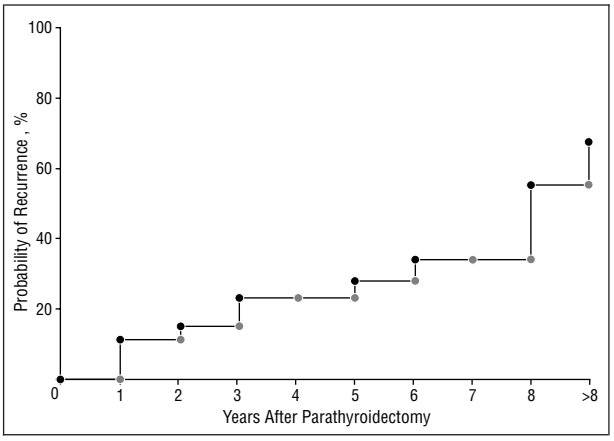
Outcome	No. (%) of Patients
Hypocalcemia	9 (24)
Normocalcemia	17 (46)
Hypercalcemia	11 (30)
Persistent	3 (8)
Recurrent	7 (19)
Indeterminate*	1 (3)

**Data were insufficient to determine whether hypercalcemia was due to persistent or recurrent disease.*

The preoperative nonparathyroid manifestations of MEN 1 (pituitary and pancreatic lesions) were not associated with calcemic outcome (**Table**). However, after adjustment for the duration of follow-up, the cumulative recurrence rates for hyperparathyroidism were 15% at 2 years, 23% at 4 years, 55% at 8 years, and 67% after 8 years (**Figure**). No patient in whom persistent or recurrent hyperparathyroidism developed within 5 years after the parathyroidectomy had an ionized calcium level less than 1.00 mmol/L (4.00 mg/dL) during the immediate postoperative period (<28 days after the operation). By comparison, 6 (67%) of 9 patients who experienced long-term disease remission had an ionized calcium level less than 1.00 mmol/L during the perioperative period (*P*=.01). For all

Patient Characteristics and Outcome of Subtotal Parathyroidectomy

Characteristic	Outcome		
	Hypocalcemia	Normocalcemia	Hypercalcemia
Women, %	44	71	73
Mean±SEM age at operation, y	42.2±3.1	33.6±2.9	35.6±3.5
Preoperative pituitary lesion, No. (%)	. . .	1 (6)	2 (18)
Preoperative pancreatic lesion, No. (%)	6 (67)	9 (53)	5 (46)
Mean ±SEM postoperative follow-up, y	4.7±1.2	3.4±0.8	7.2±1.1



Cumulative recurrence rates (determined by using the Kaplan-Meier method) of hyperparathyroidism in patients with multiple endocrine neoplasia type 1 after subtotal parathyroidectomy.

patients in whom an ionized calcium level of 1.00 mmol/L was achieved, the level was achieved within 4 days after the parathyroidectomy.

COMMENT

Our data reveal an unexpectedly high rate of recurrent hyperparathyroidism in patients with MEN 1 after subtotal parathyroidectomy. This recurrence is despite the use of an operative technique that was at least as extensive as that described by others (Table).[2,7,8,10] The size of a parathyroid gland is most appropriately expressed as tissue weight rather than volumetric measure.[14,15] For healthy subjects, Akerstrom[14] reported a mean combined weight for the parathyroid glands of 122 mg, with an upper limit of 208 mg. Normal parathyroid glands contain a substantial proportion of fat; the combined lean parenchymal mass of all parathyroid glands is therefore 87 mg, with an upper limit of 144 mg.[14] Hyperplastic parathyroid glands found in the presence of MEN 1 contain minimal amounts of adipose tissue in comparison with normal parathyroid glands.[15]

On the basis of data from Akerstrom,[14] half of a normal parathyroid gland would be expected to contain only 11 mg of parenchymal tissue. A hyperplastic gland of this mass would measure approximately 4×3×1 mm. Preserving a 4×3×1-mm tissue fragment should therefore represent the equivalent of ½ of 1 normal parathyroid gland. Our approach included the identification of all parathyroid tissue in the neck and thymus. We have attempted to retain a residuum of parathyroid gland of approximately 25 mg (eg, a quadrangular mass of 4×3×2 mm, or half of a sphere that is 5 mm in diameter).

This contrasts with the 50 to 60 mg suggested as a suitable residuum by Thompson[8] and the 60 to 80 mg advocated by Akerstrom.[14] Thus, despite leaving a smaller "half-gland" residuum than other authors, we have not achieved the high level of success heretofore described.[7,8] Two points are pertinent. First, we used the Kaplan-Meier method to compensate for the variable duration of patient follow-up. Most previous studies (in which long-term normocalcemia is reported) did not provide such an analysis.[1] Second, the ionized calcium level is more sensitive than the albumin-corrected calcium level for the early diagnosis of postoperative hyperparathyroidism.[16] Our routine use of the ionized calcium level rather than the albumin-corrected calcium level may have increased the observed cases of recurrent hyperparathyroidism. Nevertheless, the risk of recurrent PHPT does not seem to plateau with time (Figure). Thus, despite the initial postoperative normalization of the serum calcium level, recurrent hyperparathyroidism will probably develop in most patients treated with subtotal parathyroidectomy.

The factors responsible for the pathogenesis of MEN 1 parathyroid disease are poorly defined. Tissues affected by MEN 1 are of disparate embryological origin.[17] Allelic loss at the MEN 1 region of chromosome 11 is absent in up to 50% of hyperplastic parathyroid glands resected from patients with MEN 1.[18] Brandi et al[6] suggested that diffuse involvement of the parathyroid glands is the result of a circulating growth factor. Support for this contention is provided by the identification of a mitogen, believed to be basic fibroblast growth factor, in serum samples from patients with MEN 1 and hyperplasia of the parathyroid glands.[19]

Our observations indicate that even a small residuum of parathyroid tissue is capable of hyperplastic proliferation. In 1 patient who underwent exploration of the neck because of recurrent hyperparathyroidism, the estimated 25-mg residuum of the parathyroid glands (marked with a clip) that was spared at the initial parathyroidectomy had enlarged to a 1400-mg nodule during the intervening 12 years.

Two factors seem important in the hyperplastic growth and regeneration of endocrine tissue. First, normal endocrine glands contain a subpopulation of stem cells capable of clonal expansion and functional differentiation.[20] This capability is exemplified by the pathologic findings in tissue from multinodular goiter; regional differences in clonal proliferation are superimposed on a background of diffuse hyperplasia, ultimately producing the pathologic findings typical of this condition.[20] Second, as in the case of multinodular goiter, an underlying growth stimulus is necessary.[20] The high risk of recurrent hyperparathyroidism and associated enlargement of the remnant of the parathyroid glands may provide support for the concept of a circulating stimulus for hyperplasia of the parathyroid glands in MEN 1.[6]

Hypocalcemia developed after subtotal parathyroidectomy in 9 (24%) of 37 patients, although 5 (56%) of 9 patients with hypocalcemia had mild biochemical derangement and did not require vitamin D therapy. Our data indicate that older age and female sex are associated with persistent hypoparathyroidism. We observed gradual functional recovery of the parathyroid glands in some patients with MEN 1 who had postoperative hypocalcemia. In 1 patient, severe hypocalcemia developed in association with an undetectable level of parathyroid hormone after the parathyroidectomy. Supplemental calcium and vitamin D therapy were initiated, although adherence to the medication regimen was erratic. One year after the parathyroidectomy, the total and ionized serum calcium levels were 1.60 mmol/L (6.40 mg/dL) and 0.89 mmol/L (3.56 mg/dL), respectively. During the first trimester of a pregnancy (5 years after operation), the serum calcium level increased to within normal limits despite poor adherence to the medication regimen, which was subsequently discontinued. During the 11th postoperative year, a marginally elevated ionized calcium level (1.31 mmol/L [5.24 mg/dL]) was recorded.

Therefore, the propensity to recurrent PHPT in MEN 1, despite initial postoperative normocalcemia, is time and tissue-mass dependent. This dependency is an important consideration when parathyroidectomy is contemplated in young or asymptomatic patients. The optimal time for reexploration of the neck is within 3 days of the initial operation. In sporadic hyperparathyroidism, parathyroidectomy is often regarded as successful if the serum calcium level falls to within the normal range during the immediate postoperative period. Our results indicated an increased risk of persistent and recurrent hyperparathyroidism in patients in whom postoperative hypocalcemia does not develop.

A single neck exploration and subtotal parathyroidectomy may provide lifelong control of hyperpara-

thyroidism in middle-aged and elderly patients with MEN 1. In younger patients, subtotal parathyroidectomy and grafting of parathyroid tissue to the forearm musculature can be considered. If recurrent PHPT develops and graft function is adequate, another exploration of the neck and a total cervical parathyroidectomy can be undertaken. While total parathyroidectomy and autologous parathyroid tissue implantation are theoretically attractive as initial procedures, successful tissue engraftment is not consistently achieved in the presence of MEN 1.[1,10] Also, Teh et al[21] reported a high risk of malignant and atypical thymic carcinoid tumors developing in men with MEN 1. Parathyroidectomy provides an opportunity to perform prophylactic thymectomy.

CONCLUSIONS

While achievement of prolonged normocalcemia in patients with MEN 1 is markedly more difficult than in patients with sporadic hyperparathyroidism, it is possible. However, the sensitivity of the parathyroid cells to the pathophysiological mechanisms active in MEN 1 suggests that debulking procedures (with the exception of total parathyroidectomy) achieve remission rather than permanent cure of hyperparathyroidism.

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ARCHIVES OF INTERNAL MEDICINE

Hemodynamic Changes After Cardioversion of Chronic Atrial Fibrillation

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After cardioversion of chronic atrial fibrillation to sinus rhythm, there is a gradual increase of 56% in cardiac output over 4 weeks. The increase is caused by the gradual return and increasing strength of left atrial mechanical activity as the atrial myopathy of chronic atrial fibrillation subsides. Cardiac output decreases after cardioversion of atrial fibrillation in more than a third of patients, and the decrease may last a week. Acute pulmonary edema is uncommon; 50% of cases occur within 3 hours of cardioversion, with a mortality of 18%. The reduced cardiac performance after cardioversion most likely results from the combination of heart disease and cardiac depressant effects of anesthetic drugs used. Pulmonary and/or coronary artery emboli and the resumption of right atrial mechanical activity before left atrial mechanical activity may be additional factors in the pathogenesis of pulmonary edema after cardioversion. Anticoagulant therapy should be continued for a month or longer after cardioversion in those patients who maintain sinus rhythm to prevent thromboembolism. *Arch Intern Med. 1997;157:1070-1076*

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