Hyperparathyroidism Due to Single Gland Enlargement

Prospective Postoperative Study

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• **Subtotal parathyroidectomy in all patients with primary hyperparathyroidism has been proposed by several authors. Their data suggest that hyperparathyroidism may recur in up to 30% of patients treated by a conservative operation. This recurrence is attributed to chief-cell hyperplasia as the pathology in one third to one half of all patients. A conservative operation was performed on 198 hyperparathyroid patients with a single enlarged parathyroid gland between 1968 and 1970. Mild elevation of the serum calcium level was noted in two patients three months after operation. Normal serum calcium values were noted each time they were measured in the remaining patients. The present study does not support subtotal parathyroidectomy in all patients with hyperparathyroidism.**

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A prospective study of both surgically and nonsurgically treated patients with primary hyperparathyroidism was initiated at the Mayo Clinic in 1968.[1] One goal of the study was to determine how often hyperparathyroidism recurred after removal of a single enlarged gland resulting in a normal value for serum calcium. Several authors have recently suggested that multiple gland involvement or hyperplasia is the cause of primary hyperparathyroidism in from 30% to more than 50% of patients and that subtotal parathyroidectomy should be performed in all patients with this diagnosis.[2,3] We found only a single enlarged gland in 198 patients operated on between 1968 and 1970, and a probable recurrence rate of 1% in these patients at the time of this report does not support the concept of frequent involvement of multiple glands. A conservative approach to the surgical treatment of patients with primary hyperparathyroidism when only one enlarged gland is found seems justified.

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SUBJECTS AND METHODS

Between 1968 and 1970, 244 patients were treated surgically for primary hyperparathyroidism. A single enlarged gland was removed in 198 patients, and multiple enlarged glands were removed in 23 patients. In 21 patients no enlarged glands were found, and they continued to have elevated serum calcium values after operation; the results were considered negative or failed explorations. Two patients had no apparent abnormal parathyroid glands, but after surgical treatment, each patient's serum calcium value returned to normal. A vascular pedicle leading to the mediastinum was severed in one of the latter patients. The postoperative course of the 23 patients with multiple gland enlargement forms the basis of a separate communication.

Serum calcium and phosphorus levels were measured during postoperative hospitalization and three months after operation. Almost all patients whose condition was followed up subsequently had these studies performed annually. This phase of the study was completed Dec 31, 1975.

RESULTS

Surgical Procedures and Identification of Glands

Removal of one enlarged gland resulted in normal or below normal values for serum calcium during postoperative hospitalization in all 198 patients. In 70 of these 198 patients, three glands were identified as appearing normal; in 64, two glands; in 40, one gland; and in 24, no glands.

The 24 patients in whom no additional glands were identified included two who had previously undergone cervical exploration, with negative results; an enlarged gland in each patient was found at sternotomy for mediastinal exploration. Five patients had previously undergone thyroidectomy, and no attempt was made to identify additional glands once the enlarged gland was found. During thyroidectomy for multinodular goiter or Hashimoto thyroiditis, three patients were found to have a parathyroid tumor, and hypercalcemia was documented in each patient during the operation. The abnormal parathyroid was the only gland identified in 14 patients at initial cervical exploration.

Biopsy confirmation of gross identification was obtained from one gland in 36 patients, two glands in eight patients, and three glands in three patients. An entire gland of normal weight was removed as a specimen for biopsy in three patients.

Pathologic Aspects

The weight of the single glands removed ranged from 60 mg to 15 g. For the purpose of this study, a normal gland was considered to weigh less than 50 mg.

Chief cells predominated in 182 of the single enlarged glands. Nine were considered mixed-cell types, and six were primarily of oxyphil origin. There was one parathyroid carcinoma.

Two patients were members of kindreds in which hyperparathyroidism affected other family members. Two additional patients had acromegaly and a pituitary tumor, but no other family history of multiple endocrine neoplasia was known.

One patient with parathyroid carcinoma was originally operated on for hyperparathyroidism in 1962. Recurrent hypercalcemia was noted in 1968. Five grams of parathyroid tissue, considered to be malignant, were then removed, and she remained normocalcemic to the time of the most recent follow-up data, six years later.

Postoperative Serum Calcium Values

The duration of follow-up was determined from operation to the latest determination of serum calcium value (Table). Two patients with no family history of hyperparathyroidism or multiple endocrine neoplasia had normal serum calcium values on discharge from hospital (fourth postoperative day) that increased to 10.2 and 10.6 mg/dl, respectively, three months after operation (normal, 8.9 to 10.1 mg/dl). Unfortunately, both patients were then lost to follow-up.

Four patients died and 21 were lost to follow-up during the first year after operation. Serum calcium values were normal for 1 to 11 months after operation in 19. Fifteen patients died and 11 patients were lost to follow-up in the succeeding six years. In no patient with follow-up lasting more than three months was hypercalcemia known to recur. The serum calcium value was normal for 3 to 48 months after operation in each of the 19 patients who died. Serum calcium values were normal four to seven years after operation in 150 patients.

Postoperative Complications

Symptomatic hypocalcemia developed in eight patients during postsurgical hospitalization. Paresthesias and cramping of skeletal muscles affected six of the eight patients, and were attributed to "bone hunger" (increased deposition of extracellular fluid calcium in mineral-deficient hyperparathyroid bone). They all had large tumors, elevated serum alkaline phosphatase values, roentgenographic evidence of osteitis fibrosa cystica, severe hypercalcemia ($\geq$12 mg/dl), and very high levels of serum immunoreactive parathyroid hormone. In two additional patients, carpopedal spasm developed with hypocalcemia and hyperphosphatemia due to temporary hypoparathyroidism. The eight patients received oral doses of calcium, sometimes supplemented with vitamin D, for varying periods after operation. In each patient, calcium and vitamin D therapy could ultimately be discontinued, with maintenance of normal values for serum calcium and phosphate. Permanent unilateral paralysis of a vocal cord occurred in one patient who had previously undergone thyroidectomy. Pseudogout attacks occurred in two patients after operation.

COMMENT

Since the description of chief-cell hyperplasia in hyperparathyroidism by Cope and associates[4] in 1958, estimates of its prevalence have varied from 13%[1] to more than 50%.[2] Microscopic appearance alone has often been the basis for this diagnosis, even though criteria by which hyperplasia and adenoma can be differentiated by light microscopy have not been well established.[5] This lack of agreement among pathologists probably accounts for the differences in frequency with which hyperplasia is reported in the hyperparathyroid population. For this reason, we have preferred to use the terms "single" or "multiple" gland enlargement, rather than "adenoma" or "hyperplasia," based on the gross appearance and the weight of the resected glands.

In the present study, removal of a single enlarged gland restored the serum calcium to normal or below normal values in 198 patients during postoperative hospitalization. This result cannot always be equated with surgical cure, since the level of serum calcium may briefly return to normal after other surgical procedures requiring general anesthesia, or even after some negative or failed explorations. Indeed, two patients were hypercalcemic three months after operation and may have had recurrent

Postoperative Follow-Up of Primary Hyperparathyroidism With Single Gland Enlargement

Follow-up, yr	No. of Patients (N = 198)
<1	25
1-2	9
2-3	8
3-4	6
4-5	48
5-6	58
6-7	35
7-8	9

disease, though no subsequent follow-up was possible. We recognize that recurrent disease may also have developed in other patients whose postoperative follow-up data are inadequate.

Paloyan and associates[6] reported recurrent hyperparathyroidism in as many as 30% of patients with hyperparathyroidism when only a single enlarged gland was removed and the remaining glands were identified by gross inspection. Hyperplasia was described in 50% of patients,[2] leading to the recommendation that all parathyroid tissue be removed except a remnant of 50 to 100 mg in every patient with hyperparathyroidism. Sixty-five patients thus treated between 1965 and 1970 showed no evidence of recurrent hyperparathyroidism, though the duration of follow-up was not stated. Permanent hypoparathyroidism occurred in 3% of patients.[6]

Haff and Armstrong[3] described 59 patients with hyperparathyroidism, 32% of whom were considered to have chief-cell hyperplasia. Subtotal parathyroidectomy resulted in permanent hypoparathyroidism in 5%. Hypercalcemia recurred in two of five patients with hyperplasia when less than three glands were removed.

Bruining[7] encountered single gland enlargement in 134 (52.5%) of 255 patients with hyperparathyroidism operated on between 1950 and 1970. Only macroscopically enlarged glands were removed, and permanent hypoparathyroidism occurred in 1.2% of these patients. Hyperparathyroidism, possibly recurrent, developed in 2.7% of the patients.

Romanus and associates[8] found a single adenoma in 79.2% of 274 patients operated on between 1956 and 1970. Surgical treatment similar to that performed in our series led to recurrent hyperparathyroidism in 1%. Three patients had permanent hypoparathyroidism, though only one had a single enlarged gland removed.

Palmer and co-workers[9] reported single gland enlargement in 85% of 250 patients operated on between 1958 and 1973. Only grossly enlarged glands were removed. Hyperparathyroidism recurred in one patient, and two patients had permanent hypoparathyroidism. A similar experience with recurrent hyperparathyroidism was described by Muller.[10]

Block and associates[11] noted "hyperfunction in more than one parathyroid gland" in 20% of 121 patients operated on between 1960 and 1974. They advised subtotal parathyroidectomy when multiple glands were grossly enlarged, or when all parathyroids were slightly enlarged and a fifth gland was not evident, as well as when multiple endocrine neoplasia, familial hyperparathyroidism, or mild chronic renal insufficiency was diagnosed. Late recurrent hypercalcemia developed in less than 1%, and permanent hypoparathyroidism, in 4% of patients.

If primary hyperparathyroidism is due to multiple gland involvement in one third to one half of patients, as suggested by Paloyan et al[2] and Haff and Armstrong,[3] an appreciable number of patients with recurrent disease should have been encountered during our study of the results of conservative surgery. A probable recurrence rate of 1% and no instances of permanent hypoparathyroidism appear to support our conservative approach to treatment when a single enlarged gland is found.

Many patients with hyperparathyroidism are discovered during serum screening procedures in the course of routine health examinations, and have primarily biochemical evidence of the disease. Surgery in many of these patients is undertaken prophylactically. In this group, as well as in those patients with symptoms or complications of the disease, it is important to remove only the amount of parathyroid tissue necessary to restore the serum calcium value to normal and to avoid recurrent hyperparathyroidism or permanent hypoparathyroidism.

The rationale for subtotal parathyroidectomy in the presence of multiple enlarged glands, especially when coexisting with multiple endocrine neoplasia, familial hyperparathyroidism, or chronic renal insufficiency, is well established. If hyperparathyroidism recurred often after the removal of a single enlarged gland when the remaining identified glands appeared normal in size, justification for subtotal parathyroidectomy in the presence of enlargement of a single gland would exist. We do not believe the results of the present study support such surgical recommendations.

The decision concerning the extent of parathyroidectomy should be made by the surgeon for each patient, based on the number, location, and gross appearance of the identified glands, as well as on information concerning possible coexisting factors that may predispose to multiple gland involvement. The wisdom of the decision becomes evident when long-term postoperative results are studied for the frequency of persistent or recurrent hyperparathyroidism and permanent hypoparathyroidism.

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Discussion

MELVIN A. BLOCK, MD, Detroit: Dr Purnell and his associates have presented a massive experience that should place in proper perspective the clinical significance of multiple gland involvement in primary hyperparathyroidism. The evidence appears overwhelming that single gland involvement is by far the predominant abnormality, that removal of the gland controls the disease in more than 99% of patients; and that routine, or even frequent, subtotal parathyroidectomy is not needed or justified.

Our experience agrees with theirs except that multiple gland involvement has been slightly greater, present in approximately 20% of patients with primary hyperparathyroidism. This is probably due to our relatively greater frequency of patients with multiple endocrine neoplasms and familial hyperparathyroidism. We also agree that the reported variations in multiple gland involvement relate to variations in the number of patients with predisposing factors, as well as in interpretation of microscopic findings by pathologists, there being a lack of precise criteria for hyperplasia. Late recurrence of hypercalcemia develops in less than 1% of patients in our experience also. This low figure now appears to be well established.

Of interest is that the first two patients recorded to have had operation on the parathyroid glands for primary hyperparathyroidism demonstrated the two major problems that still plague surgeons. First, the patient for whom Mandl removed a parathyroid tumor had multiple gland involvement demonstrated by the finding of a second parathyroid tumor at autopsy, which followed an unsuccessful second neck operation. All are familiar with the other patient, Captain Martell, in whom the parathyroid tumor located in the mediastinum was so elusive.

Multiple gland involvement, although not frequent, is, however, a real problem. Persistent hypercalcemia following operations has been more common than late recurrence. In our experience, at least two thirds of patients with multiple gland involvement have demonstrated predisposing factors. The remaining patients, including those rare ones with only slight enlargement of all parathyroids, make necessary the evaluation of all parathyroid operations. We advocate selective subtotal parathyroidectomy for patients known to have predisposing characteristics and those in whom more than one gland is found to be enlarged. Recording weights of parathyroid glands removed is important.

Relative to terminology, we would like to support the terms "single" and "multiple" gland involvement in characterizing patients with primary hyperparathyroidism. We, too, have become disenchanted with the terms "adenoma" and "hyperplasia." In the past, we utilized designations of single or multiple tumors of parathyroids, but agree that the terminology suggested in this report is preferable.

I would appreciate comments from Drs Purnell and Beahrs on two items. First, in their report are mentioned 23 patients in whom multiple gland involvement was found. Does this group include any patients in whom at the initial operation only a single gland was removed, and the patient thought to represent single gland involvement? Second, 21 patients were recorded as possessing no abnormal parathyroid glands, but hypercalcemia persisted postoperatively. Although this is a separate and significant matter, did they observe any major characteristic of this group?

J. ENGLEBERT DUNPHY, MD, San Francisco: I would support the authors' thesis from data compiled at the University of California by a late member of this society, Dr Leon Goldman, Dr Thomas Hunt, and a junior colleague of ours, Dr Orlo Clark. In this entire group, the recurrence rate from 295 patients was 3.7%. In accordance with what has been said earlier today, in patients with multiple endocrine adenomatosis or familial hyperparathyroidism, there was a recurrence rate of 33%. The same is true in parathyroid cancer.

However, if the initial operation, regardless of diagnosis, was done in our department, the overall recurrence rate was 2.7%, indicating that if you routinely expose all four, or sometimes five, glands, the overall recurrence rate will be low, and if we eliminate endocrine adenomatosis or familial hyperparathyroidism, the overall recurrence rate was 0.4%. Certainly, under these circumstances, if one is capable of thoroughly dissecting out each parathyroid, there is no indication for radical subtotal removal as a routine.

DR BEAHRS: This presentation deals with the 198 patients in whom single gland involvement was present. The 23 patients with multiple gland involvement and the 21 patients in whom no pathologic change was found, all undergoing surgery between 1968 and 1970, are the subject of a second study.

Of the patients who had persistent hypercalcemia following exploration, in 70% of cases all four glands were identified. However, no pathologic condition was found. In these instances, one might assume that some other pathologic change was responsible for the hypercalcemia, or that more than four parathyroid glands were present, or possibly that the diagnosis was in error. Today, however, with accurate laboratory determinations and ability to determine the parathyroid hormone levels, a misdiagnosis is unlikely.

In a recently reported study, the success rate of finding pathologic changes in the parathyroid at cervical exploration without the aid of sophisticated tests was 96% in primary cases and 75% in secondary cases.

We believe the data in this study support the facts that: (1) primary hyperparathyroidism is a single gland disease in 90% of patients; (2) removal of the one gland in these patients results in a cure of hypercalcemia in all except 1% or fewer; (3) pathologic changes in the parathyroid are not a reflection of hyperplasia or multiple gland involvement, except in a minority of patients; and (4) widespread use of 3½ gland resection or subtotal parathyroidectomy is not justified and should be used in only selected patients in whom the pathologic condition obviously involves more than one gland, or in patients with familial conditions.