

Persistent Hypercalcemia After Neck Exploration – An Analysis of 34 Cases

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Summary. A retrospective analysis of 34 patients undergoing 45 re-explorations for persistent hypercalcemia is presented. Thirteen out of the 20 enlarged parathyroid glands were found at reoperation to be normally located, indicating that the initial exploration had been incomplete. A follow-up study of the reoperated patients showed that 25 (74%) were normocalcaemic. Three patients had permanent unilateral recurrent laryngeal nerve damage and 2 patients required calcium and/or vitamin D therapy. Ultrasonography was effective in the diagnosis and localisation of residual parathyroid adenoma in patients with persistent postoperative hyperparathyroidism.

Key words: Persistent hypercalcemia, Parathyroid adenoma, Preoperative localization.

Introduction

The first operation for parathyroid disease was carried out in 1925 by Mandl but the operation failed to reverse the hypercalcemia. Ever since, persistent hyperparathyroidism after cervical exploration has been a significant clinical problem. Persistent hypercalcemia occurs in about 5–10% of patients undergoing neck exploration and most of them have a second operation [3, 5, 8, 10, 13]. Since reoperation carries a relatively high risk of complications, more knowledge about the surgical management of hyperparathyroidism would minimize the need for re-exploration. This paper presents an analysis of 34 patients with persistent hypercalcemia treated at our hospital between 1961 and 1983.

Patients and Methods

34 patients (22 women and 12 men with a median age of 62 years) underwent 45 reoperations for persistent hypercalcemia. Seven of

the patients had 2 reoperations and 2 patients had 3 reoperations. Twenty-four of the patients underwent the primary operation in our hospital and 10 were initially operated on in other surgical clinics.

The initial neck exploration was performed by 19 different surgeons with varying degrees of experience in endocrine surgery. Preoperative freeze-section technique was not available at 8 of the explorations. Four glands were identified in 3 patients, 3 glands in 10 patients, 2 glands in 7 patients, 1 gland in 5 patients and in 9 patients no parathyroid was identified. Thyroid resection was carried out in 13 patients (of whom 10 were resected bilaterally) and complete thymus dissection was performed in only 5 patients.

The initial histopathological diagnoses were made by different pathologists and a review of all specimens was made by one pathologist using hematoxylin eosin, periodic acid-Schiff (P.A.S.) and fat stains.

Results

15 patients complained of fatigue and mental disturbances, renal symptoms predominated in 8 patients and gastrointestinal symptoms were evident in 6 patients. Three patients were referred because of hypercalcemic crisis and 6 patients were completely asymptomatic at the time of re-exploration. Median serum calcium concentration was 3.0 mM and median serum phosphate concentration was 0.8 mM.

In 22 patients one or more attempts were made to localize the diseased parathyroid tissue preoperatively (Table 1). In our experience ultrasonography and computed tomography (CT) were reliable in the diagnosis of parathyroid enlargement. The accuracy of ultrasonography, in 5 patients, was 80%.

Surgical Findings

Six different surgeons performed the 45 re-explorations. At operation, 20 single, enlarged parathyroid glands (12 adenomas and 8 hyperplastic glands) were found in 18 patients. Thirteen of these adenomatous/hyperplastic glands

Table 1. Results of different methods for preoperative localization of pathological parathyroid glands in 22 cases with persistent postoperative hypercalcemia

Method	Number or investigations	Number of correct localizations
Angiography	12	3 (25%)
Venous sampling with iPTH determination	15	5 (33%)
Selenium scintigraphy	1	0 (0%)
Ultrasonography	5	4 (80%)
CT-scan	4	3 (75%)

Table 2. Comparative pathology of removed parathyroid tissue at initial exploration and final reoperation in 34 patients with persistent hypercalcemia. Figures within brackets indicate number of patients

Initial operation	Reoperation
Adenoma ± normal gland (6)	Chief cell hyperplasia (3) Adenoma (2) No specimen (1)
Nodular hyperplasia (3)	Nodular hyperplasia (2) No specimen (1)
Chief cell hyperplasia (9)	Chief cell hyperplasia (3) Adenoma (1) No specimen (5)
Water clear cell hyperplasia (1)	Water clear cell hyperplasia (1)
Normal gland (4)	Adenoma (3) No specimen (1)
No specimen (10)	Adenoma (4) Nodular hyperplasia (1) Normal gland (1) No specimen (4)
Unknown (1)	No specimen (1)

were of normal position, 3 were found in the thymus, 2 were located within the thyroid, 1 was located behind the oesophagus and 1 large adenoma was found in the anterior mediastinum (via sternotomy). Two – three hyperplastic glands were removed from 2 patients and in 14 patients no pathologically altered glands were detected at all.

Eight sternotomies were performed and one parathyroid adenoma was retrieved.

The histopathological diagnoses in the reoperated patients are shown in Table 2 which also demonstrates the diagnoses made at the initial exploration.

Early and Late Results of Reoperation

A flow chart of the early surgical results is shown in Fig. 1. Altogether, surgery cured 23 patients of hypercalcemia.

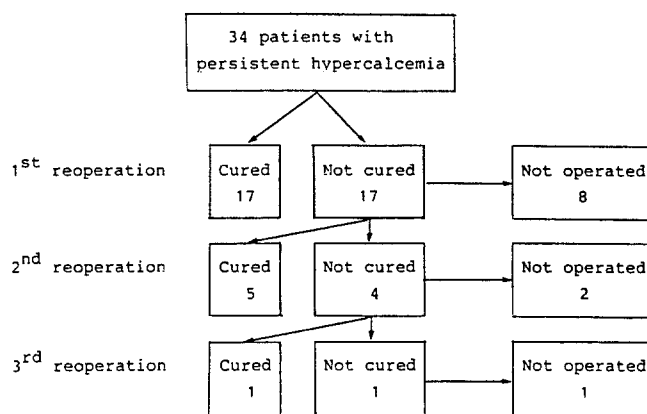


Fig. 1. Flow chart of the early surgical results in 34 patients operated on for persistent hyperparathyroidism

Three of these patients were cured despite the fact that no pathological gland was found at the exploration. Follow-up investigation (> 1 year postoperatively) showed that 21 patients were normocalcemic without medication and that 2 patients were normocalcemic with supplementary calcium and/or vitamin D.

Ten of 11 patients who were discharged with hypercalcemia were reviewed 1–23 years postoperatively. Two became normocalcemic without any symptoms of disease, one had borderline hypercalcemia and two were successfully operated on elsewhere. Four patients died of unrelated diseases (colonic neoplasm, chronic nephritis and cardiovascular disease) while hypercalcemic. One who remained hypercalcemic suffers from muscular weakness and may undergo further re-exploration.

In seven of the hypercalcemic patients in this series, the diagnosis of hyperparathyroidism was never established either because no specimen was retrieved or because only normal glands were removed at operation. In only two of these cases, however is the diagnosis of hyperparathyroidism unlikely.

Three patients suffered permanent unilateral paralysis of the recurrent laryngeal nerve following re-exploration. These patients were reoperated once only.

Discussion

The most important cause of persistent hypercalcemia after parathyroid surgery seems to be an inadequate primary exploration [12, 13]. This observation was confirmed in the present study which showed that 13 out of 20 missed adenomas were found at completely normal locations in the neck and that another 3 adenomas were situated in the thymus. However, some adenomas were located at extraordinary sites along the embryonic pathways for parathyroid gland descensus, implying that the therapeutic failure sometimes can be due to insufficient knowledge of parathyroid embryology rather than to surgical skill.

When comparing the microscopic findings in the parathyroid tissue removed at the initial operation with that obtained at reoperation (Table 2) it is evident that double adenomas exist but are rare (about 3% of all patients with primary hyperparathyroidism operated on in our hospital). The comparison also supports the notion that the distinction between nodular hyperplasia and adenoma is difficult and that subtotal parathyroidectomy is advocated in the former cases.

When faced with a patient with persistent postoperative hypercalcemia one has to decide whether or not reoperation is necessary. Most authors suggest that only patients with deteriorating renal function or severe clinical symptoms should be re-explored [5, 8, 10] but a more liberal policy would be justified if it was possible to locate the diseased tissue preoperatively. Several methods have been reported but the successful outcome seems to vary considerably depending on the experience of the investigator [2, 10, 14]. However, in recent years ultrasonography has proved to be a very reliable method to visualise enlarged parathyroid glands (80% success rate in this series) and this procedure is free from complications [1, 4, 6, 11]. CT-scan has also provided some promising results especially in the detection of mediastinal adenomas [2, 7].

If previous surgery has failed to localize all parathyroid glands, the surgical approach at reoperation should be directed towards the neck. If an adenoma is found and histologically verified on the first explored side we believe that there is no need for further dissection. If no abnormal glands are encountered at the normal sites, a proper dissection of the thymus should be performed. This dissection can usually be carried out via the Kocher incision. Sternotomy, on the other hand, has been reported to be unnecessary in most cases [9, 12] and this also holds true for the present series in which, in retrospect, only one out of 8 sternotomies turned out to be successful.

Repeated parathyroid surgery carries a substantial morbidity in comparison to the primary exploration, mainly due to hypoparathyroidism and to the risk of nerve damage. No postoperative deaths were encountered in our series but 2 patients had permanent hypocalcemia and another 3 patients had permanent nerve damage. These morbidity figures are comparable to those reported by others [5].

Surprisingly, at follow-up we found 3 patients who were normocalcemic although they had been discharged in a hypercalcemic state. The explanation might be that the diagnosis was incorrect but the possibility of an impairment of the vascular supply to the parathyroid glands during surgery also remains. However, this observation emphasized the opinion that re-exploration of patients with persistent hypercalcemia should be delayed until at least 6 months have elapsed after the last operation.

In conclusion, reoperation for persistent hyperparathyroidism can often be avoided if the initial operation is based on an adequate diagnosis and performed by an experienced surgeon with access to facilities for frozen section examination. When reoperations are necessary they should be performed at centers where both diagnostic and surgical experience are available.

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