World J. Surg. 10, 668–672, 1986

World Journal of Surgery

Parathyroid Surgery in the Multiple Endocrine Neoplasia Type I Syndrome: Choice of Surgical Procedure

Jan Malmaeus, M.D., Lars Benson, M.D., Henry Johansson, M.D., Sverker Ljunghall, M.D., Jonas Rastad, M.D., Göran Åkerström, M.D., and Kjell Öberg, M.D.

Departments of Surgery, Medicine, and Clinical Chemistry, University Hospital, Uppsala, Sweden

Thirty-nine patients with hyperparathyroidism (HPT) in association with the multiple endocrine neoplasia type I (MEN-I) syndrome underwent parathyroid surgery from 1961 to 1985. Twenty-one patients underwent resection of 1–2½ glands, 6 had 3–3½ glands removed, and 18 (9 of whom had previously been subjected to parathyroid surgery) underwent total parathyroidectomy with autotransplantation to the forearm. Resection of 1–2½ glands resulted in persistent or recurrent HPT in 18 (88%) of the 21 cases. Two (33%) of the 6 patients who underwent 3–3½-gland resection had recurrent disease. After total parathyroidectomy with autotransplantation to the forearm, no patient had persistent or recurrent HPT. Five (26%) of 18 patients had permanent hypocalcemia requiring supplemental therapy. After a change in the operative technique, however, only 1 of 10 was permanently hypocalcemic. It is concluded that primary HPT in the MEN-I syndrome always should be treated with radical surgery. Total parathyroidectomy with autotransplantation seems more favorable than 3–3½-gland resection owing to the absence of recurrent HPT in this material and the limited number of patients with long-standing postoperative hypocalcemia, provided that an optimal technique for autotransplantation was performed.

Primary hyperparathyroidism (HPT) of the multiple endocrine neoplasia type I (MEN-I) syndrome is characterized by hyperplasia of the parathyroid glands with an asymmetrical glandular enlargement [1–4]. Prior to the recognition of a multiglandular disease, patients with HPT in the MEN-I syndrome were often subjected to extirpation of single glands, whereas most authors nowadays advocate subtotal or total parathyroidectomy [5–7]. The different procedures of surgery in these patients have all been associated with a considerable rate of recurrence [6–9]. This may reflect the perioperative difficulties in adequately determining the extent of the parathyroid disease and probably also a genetically determined increase in growth potential of the parathyroid tissue in these patients.

The present study of patients with HPT associated with the MEN-I syndrome was performed to analyze the outcome of parathyroid surgery in relation to different operative procedures and with special reference to total parathyroidectomy with immediate autotransplantation to the forearm.

Materials and Methods

The material consisted of 39 patients with primary HPT (19 females, 20 males) originating from 12 kindreds with a verified MEN-I syndrome. The patients were 20–63 years old (mean 41 yr). In addition to HPT, 12 patients had a pancreatic tumor, 6 had a pituitary tumor, and 6 had both a pancreatic and pituitary tumor. The preoperative values of serum calcium varied between 2.61 mmol/l and 3.31 mmol/l (mean 2.81 mmol/l).

Thirty of the patients were primarily operated on at 8 different hospitals from 1961 to 1982. A resection of 1–2½ glands was performed in 21 of them, 3–3½ glands were extirpated in 6, while, in 3 patients, 4 parathyroid glands were inadvertently removed without an autologous transplantation. The number of glands identified at the operation of

Presented at the International Association of Endocrine Surgeons in Paris, September 1985.

Supported by the Swedish Medical Research Council.

Reprint requests: J. Malmaeus, M.D., Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden.

Table 1. Number of glands identified in patients subjected to resection.

	Resection of 1–2½ glands	Resection of 3–3½ glands	Resection of 4 glands without autotransplantation	Resection of 4 glands with autotransplantation
≥4 glands	5	5	3	16
3 glands	11	1		2
2 glands	4			
1 gland	1			
Total	21	6	3	18

Table 2. Outcome of surgery in patients subjected to resection.

	Resection of 1–2½ glands	Resection of 3–3½ glands	Resection of 4 glands without autotransplantation	Resection of 4 glands with autotransplantation
Normocalcemia	2	4	–	13
Hypocalcemia[a]	1	–	3	5
Hypercalcemia				
Persistent	5	–	–	–
Recurrent	13	2	–	–
Total	21	6	3	18

[a]Hypocalcemia refers to patients requiring permanent postoperative substitution.

these patients is shown in Table 1. They were followed for 1–14 years (mean 6.5 yr) after the operation.

Total parathyroidectomy with autotransplantation was performed at our surgical clinic in 18 patients from 1981 to 1985. Nine of these patients had been previously operated on with 1–3½-gland resections. A total of at least 4 parathyroid glands were identified in 16 of them while 3 glands were located in the remaining 2 cases (Table 1). The surgical procedure involved a cervical thymectomy and a wide excision of fat tissue surrounding the parathyroid glands [10]. In the first 8 patients, 50–60 mg of parathyroid tissue was inserted in about 20 pieces of 1 mm^3 into the brachioradial muscle [11]. Due to a high incidence of postoperative hypocalcemia, the amount of transplanted tissue was increased to approximately 60–70 mg in the last 10 patients. To facilitate vascular ingrowth, the size of each implant was reduced from 1 to ½ mm^3 and thus, the number of implants was increased from 20 pieces to between 40 and 50, placing 2 pieces in each pocket. The patients subjected to total parathyroidectomy and autotransplantation have been followed for 4–43 months (mean 23 mo).

Results

In the 21 patients subjected to 1–2½-gland resections, the surgeon suspected an adenoma primarily because of an insufficient visualization of the parathyroids and a considerable asymmetry in glandular enlargement. Among the 18 patients in whom 3 or more parathyroid glands were extirpated during 1 operation, the largest gland had an average weight of 650 mg while that of the smallest was 75 mg. In each individual case, the weight relation between these glands was 8–9 to 1 mg.

After resection of 1–2½ glands, 2 patients were normocalcemic at follow-up without substitution therapy while 1 patient needed vitamin D to maintain normal levels of serum calcium (Table 2). Five patients had persistent HPT and 13 others suffered from hypercalcemia recurring 1–13 years (mean 5 yr) after the operation. Among the 6 patients in whom 3–3½ glands were excised, 4 had a normal serum calcium value 1–7 years (mean 4 yr) after operation, while 2 patients recurred 3 and 14 years after the exploration (Table 2). All the patients subjected to a total parathyroidectomy without autotransplantation required permanent vitamin D substitution due to hypoparathyroidism (Table 2). In these cases, the surgeon had gradually removed normal-sized and slightly enlarged glands until the 4th and largest gland was located.

The follow-up of the 18 patients undergoing a total parathyroidectomy and autotransplantation revealed that none of them had signs of persistent or recurrent HPT (Table 2). The postoperative reduction in serum calcium was considerable (Fig. 1). The lowest values were generally attained 2–3 days after the operation although, in some cases, the serum calcium level gradually decreased during the first 2 postoperative weeks. All but 2 patients re-

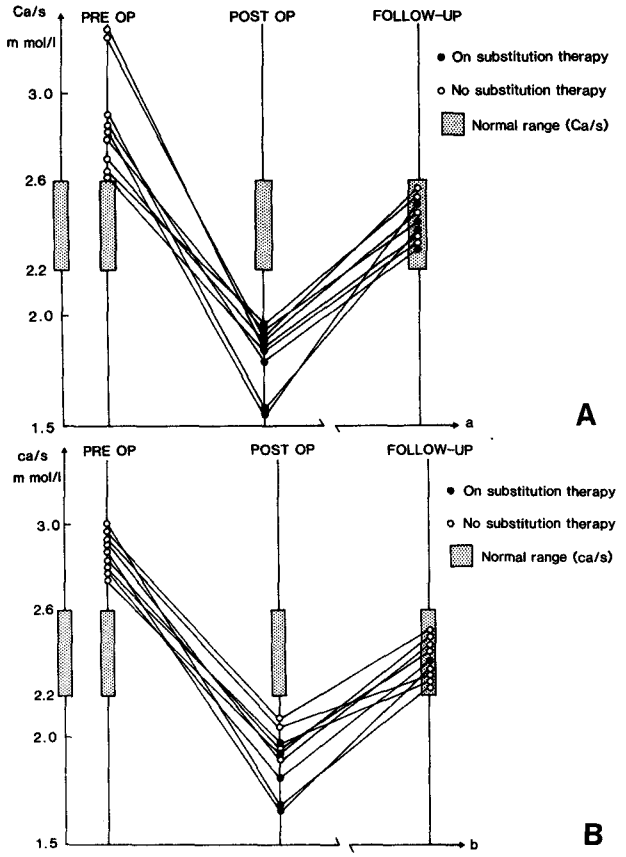

Fig. 1. Serum calcium values preoperatively, during the immediate postoperative period, and at follow-up after total parathyroidectomy and immediate autotransplantation in 18 patients. **A.** Primary operations (n = 9). **B.** Secondary operations (n = 9).

quired substitution with vitamin D and/or oral calcium for 2–8 months. The medication was maintained in 5 patients but the doses of vitamin D had been reduced and the calcium tablets withdrawn in 3 of them. Since the technical alteration in autotransplantation was introduced, only 1 of 10 patients has required a permanent supplementation medication.

Discussion

In this study, a relation was found between the extensiveness of parathyroid surgery and the incidence of persistent and recurrent HPT. Among patients subjected to excision of 1–2½ glands, 24% suffered from persistent and 62% from recurrent hypercalcemia, while recurrences were found in 33% of those operated on with 3–3½-gland resections. Some of these recurrences occurred after considerable periods of time which is similar to the findings in patients with nonfamiliar primary hyperplasia (C. Rudberg et al., unpublished data).

The results show that total parathyroidectomy with immediate autotransplantation effectively reverses the hypercalcemia of HPT associated with the MEN-I syndrome. Among 18 patients operated on, none showed signs of persistent or recurrent HPT during an average follow-up of about 2 years. This is in contrast to the findings of Wells et al. [6] describing a graft-dependent hypercalcemia in 8 of 16 patients with HPT in association with the MEN-I and II syndromes. Although our time of follow-up is short, the reason for the discrepancy in the incidence of postoperative hypercalcemia is unclear. It may depend on differences in the patient materials. We usually operate on our patients at an early stage when moderate increases in the serum calcium levels are found. Also many of our patients are young, which might account for the different results. It could also be that the genetic trait varies in aggressiveness among different patients and perhaps also among different kindreds. This is evidently the case for involvement of the endocrine pancreas [12] but possibly also for parathyroid disorders. The majority of recurrences, therefore, occurred within the first 2–3 years, but 3 patients undergoing only 1-gland resection did not recur until 12, 13, and 14 years after operation, respectively. This hypothesis is now being subjected to further study.

The frequency of hypocalcemia in the short-term postoperative course was high in the patients subjected to total parathyroidectomy and autotransplantation. All but 2 of them required temporary supplementation therapy to maintain acceptable levels of serum calcium. This demonstrates the radicality of surgery and absence of residual parathyroid tissue after the operations. In this context, the importance of a cervical thymectomy and a wide excision of fat tissue surrounding the parathyroids in order to remove supernumerary and lobated glands [10, 13] should be emphasized. Among the patients operated on with the primary method of autotransplantation, 4 of 8 required permanent supplementation therapy, while this was necessary in only 1 of 10 of those subjected to the insertion of smaller but more numerous pieces of parathyroid tissue. It seems, therefore, as if function and vascular ingrowth may be facilitated by a size reduction of the grafted pieces [14]. The transplants were generally removed from the smallest gland since this may exhibit the least deranged regulation of parathyroid hormone release and cell growth within the parathyroid tissue of each patient (L. Benson et al., unpublished data).

In accordance with previous studies [1, 3, 6, 15], therefore, the present study indicates that primary HPT in the MEN-I syndrome should be treated with radical parathyroid surgery. Total parathyroidecto-

my with autotransplantation seems more favorable than subtotal resection owing to the absence of recurrent HPT in this material and the limited number of patients with long-standing postoperative hypocalcemia, provided an optimal technique for autotransplantation was applied.

Résumé

Trente-neuf malades atteints d'hyperparathyroïdisme associé à un syndrome MEN-I ont subi une intervention parathyroïdienne entre 1961 et 1985. Chez 21 d'entre eux il fut procédé à l'ablation de 1–2½ glandes, chez 6 à l'ablation de 3–3½ glandes, chez 18 à une parathyroïdectomie totale complétée par une transplantation de tissu parathyroïdien dans l'avant bras (9 de ces derniers avaient déjà été soumis à une intervention sur les parathyroïdes). La résection de 1–2½ glandes s'est soldée par une hyperparathyroïdie persistante ou récidivante dans 18 (88%) des 21 cas, celle de 3–3½ glandes par le même phénomène chez 2 (33%) des 6 opérés. En revanche après parathyroïdectomie totale suivie d'autotransplantation dans l'avant bras aucun cas d'hyperparathyroïdisme persistant ou récidivant ne se manifesta. Cinq sur 18 malades qui présentèrent une hypocalcémie permanente nécessitèrent un traitement complémentaire; cependant après modification de la technique opératoire seulement 1 sur 10 des malades accusa une hypocalcémie permanente. On peut conclure de ces faits que l'hyperparathyroïdisme associée à un syndrome MEN-I doit toujours être traité par chirurgie radicale. Dans cette série la parathyroïdectomie totale avec autotransplantation paraît supérieure à la résection de 3–3½ glandes en raison de l'absence de récidive de l'hyperparathyroïdie et du nombre limité de patients présentant une hypocalcémie postopératoire de longue durée dès lors que l'autotransplantation est réalisée suivant la meilleure technique.

Resumen

Treinta y nueve pacientes con hiperparatiroidismo (HPT) asociado con el síndrome de neoplasia endocrina múltiple tipo 1 (NEM-1) fueron sometidos a cirugía paratiroidea entre 1961 y 1985. Veinte y uno casos tuvieron resección de 1–2½ glándulas, 6 casos tuvieron resección de 3–3½ glándulas, y 18 casos (9 de los cuales habían sido previamente sometidos a cirugía paratiroidea) tuvieron paratiroidectomía total con autotransplante en el antebrazo. La resección de 1–2½ glándulas resultó en HPT persistente o recurrente en 18 (88%) de los 21 casos. Dos (33%) de los 6 pacientes que tuvieron resección de 3–3½ glándulas desarrollaron enfermedad recurrente. Ninguno de los pacientes sometidos a paratiroidectomía total con autotransplante en el antebrazo exhibió HPT persistente o recurrente. Cinco (26%) de 18 pacientes presentaron hipocalcemia permanente que requirió terapia de suplencia. Después de una modificación en la técnica operatoria, sinembargo, sólo 1 de 10 apareció con hipocalcemia permanente. Se llega a la conclusión de que el HPT primario en el síndrome NEM-1 siempre debe ser manejado con cirugía radical. La paratiroidectomía total con autotransplante parece ser más favorable que la resección de 3–3½ glándulas debido a la ausencia de HPT recurrente en esta serie y al limitado número de pacientes con hipocalcemia postoperatoria de larga duración siempre y cuando se emplee una técnica óptima para el procedimiento de autotransplante.

References

1. Lamers, C.B.H.W., Froeling, P.G.A.M.: Clinical significance of hyperparathyroidism in familial multiple endocrine adenomatosis type I (MEA-I). Am. J. Med. *66*:472, 1979
2. Yamaguchi, K., Kameya, T., Abe, K.: Multiple endocrine neoplasia type 1. Clin. Endocrinol. Metab. *9*:261, 1980
3. Prinz, R.A., Ganvros, O.I., Sellu, D., Lynn, J.A.: Subtotal parathyroidectomy of primary chief cell hyperplasia of the multiple endocrine neoplasia type-I syndrome. Ann. Surg. *293*:26, 1981
4. Thompson, N.W.: Surgical considerations in the MEA 1 syndrome. In Endocrine Surgery, I.D.A. Johnston, N.W. Thompson, editors. London, Butterworths International American Reviews, 1983, pp. 174–183
5. Edis, A.J., van Heerden, J.A., Scholz, D.A.: Results of subtotal parathyroidectomy for primary chief cell hyperplasia. Surgery *86*:462, 1979
6. Wells, S.A., Jr., Farndon, J.R., Dale, J.K., Leight, G.S., Dilley, W.G.: Long-term evaluation of patients with primary parathyroid hyperplasia managed by total parathyroidectomy and heterotopic autotransplantation. Ann. Surg. *192*:451, 1980
7. van Heerden, J.A., Kent, R.B., Sizemore, G.W., Grant, C.S., Remine, W.H.: Primary hyperparathyroidism in patients with multiple endocrine neoplasia syndromes. Arch. Surg. *118*:533, 1983
8. Clark, O.H., Way, L.W., Hunt, T.K.: Recurrent hyperparathyroidism. Ann. Surg. *184*:391, 1976
9. Rizzoli, R., Green, J., Marx, S.J.: Primary hyperparathyroidism in familial multiple endocrine neoplasia type I. Am. J. Med. *78*:467, 1985
10. Åkerström, G., Malmaeus, J., Bergström, R.: Surgical anatomy of human parathyroid glands. Surgery *95*:14, 1984
11. Wells, S.A., Jr., Gunnels, J.C., Schelborne, J.D., Schneider, A.B., Sherwood, C.M.: Transplantation of the parathyroid glands in man: Clinical indications and results. Surgery *78*:34, 1975
12. Öberg, K., Wålinder, O., Boström, H., Lundqvist, G., Wide, L.: Peptide hormone markers in screening

for endocrine tumors in multiple endocrine adenomatosis type I. Am. J. Med. *73*:619, 1982
13. Malmaeus, J., Åkerström, G., Johansson, H., Ljunghall, S., Nilsson, P., Selking, Ö.: Parathyroid surgery in chronic renal insufficiency. Acta Chir. Scand. *148*:229, 1983
14. Saxe, A.: Parathyroid autotransplantation: A review. Surgery *95*:507, 1984
15. Scholz, D.A., Purnell, D.C., Edis, A.J., van Heerden, J.A., Woolner, L.B.: Primary hyperparathyroidism with multiple parathyroid gland enlargement. Mayo Clin. Proc. *53*:792, 1978

Invited Commentary

Jon A. van Heerden, M.D.

Department of Surgery, Mayo Clinic, Rochester, Minnesota, U.S.A.

Ever since the "birth" of parathyroid surgery in 1925, the surgeon has been bedevilled by the delicate balance that exists between excising a sufficient amount of abnormal parathyroid tissue which renders the patient eucalcemic and protected from recurrent/persistent hypercalcemia, on one hand, and excising excessive parathyroid tissue rendering the patient hypocalcemic, on the other. Although this balancing act is important for all patients with hyperparathyroidism, it is particularly important in those patients who have hyperparathyroidism as a manifestation of the multiple endocrine neoplasia type I (MEN I) syndrome.

Four questions add to the frustration when managing those patients with the MEN I syndrome:

1. Is the parathyroid pathologic state encountered invariably hyperplasia? It is certainly tempting to assume that, in concert with the traditional pathologic condition found in the endocrine glands affected in these patients, the pathologic findings should be both diffuse and multicentric. What *is* known is that the parathyroid enlargement in MEN I patients is very uneven and that a normal-sized gland may indeed be functionally overactive. In addition, in series in which patients with MEN I were surgically treated as if they had single-gland (adenomatous) disease, the incidence of persistent or recurrent hypercalcemia has been unacceptably high (24% in our experience and 88% in the experience of the authors). We should thus, I believe, correctly assume that the parathyroid glands are diffusely hyperplastic in patients with the MEN I syndrome.

2. What is the stimulus for the hyperplasia? This is a most intriguing question—the answers to which are purely conjectural in nature. As students, we have to ponder whether an as yet unidentified renotubular defect of calcium/phosphorus excretion exists and whether there really ever is a situation termed primary parathyroid hyperplasia. Is, in fact, all hyperparathyroidism, be it sporadic or MEN related, secondary in nature?

3. Which should be performed, total versus subtotal parathyroidectomy? Parathyroid surgeons are today firmly divided into 2 camps regarding the extent of parathyroidectomy in these patients. We, and others, have continued to practice subtotal parathyroidectomy being both happy with the long-term eucalcemia rate (93%) and unhappy with the high incidence of graft-dependent hypercalcemia (50%) reported by Wells et al. in 1980.

4. Is the percentage of supernumerary glands increased in MEN I patients? There is little, if any, disagreement that this is so. A figure of 12–15% should be anticipated. It is for this reason that the authors correctly emphasize that a transcervical thymectomy should be an integral part of the surgical procedure in all of these patients, regardless of the number of parathyroid glands found in the neck.

The authors are to be congratulated for providing us with a unique and authoritative review of their experience comparing different surgical approaches to the problem. Their results with total parathyroidectomy and immediate autotransplantation (40–50 implants of ½-mm^3 size) is the best reported to date, and should force all subtotal parathyroidectomists to reevaluate their current philosophy. This reviewer, though, would add a cautionary note: The authors' patients treated by total parathyroidectomy have been followed for a mean of only 23 months—in view of the snail's pace at which the evolution of overt hyperparathyroidism occurs, it is too soon to sound the last hurrah regarding the surgical treatment of this fascinating subgroup of patients with hyperparathyroidism. We shall await, with eager anticipation, further follow-up data from our colleagues in Uppsala.