Reoperation for persistent or recurrent secondary hyperparathyroidism. Surgical treatment of renal hyperparathyroidism

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Summary. Background: Secondary hyperparathyroidism is a common acquired disorder seen in chronic renal failure. Its pathophysiology is mainly due to hyperphosphatemia and vitamin D deficiency and resistance. When medical treatment fails, subtotal and total parathyroidectomy with autotransplantation are the standard procedures, although both are associated with high recurrence rates.

Methods and Results: 4 patients experienced persistence and 9 relapse. The first 4 were subjected to reoperation after 6 months for the persistence of symptoms due to the finding of a supernumerary adenomatous gland while the remaining patients at the reoperation showed in 5 cases 2 more glands in over thymic position, and 4 an hyperplasia of the residual glandular tissue. A classic cervicotomy was sufficient to remove the residual parathyroid in patients with persistent hyperparathyroidism. For cases of recurrent hyperparathyroidism it was enough a medial approach and sometimes lateral for the complete excision of the hyperplastic tissue. The advent of the intraoperative technique of parathyroid hormone dosage allowed a better performance of the surgical technique for the last 3 patients undergoing reoperation. After reoperation all patients had immediate regression of clinical symptoms with normalization of serum calcium and PTH levels.

Conclusions: On the basis of these considerations, diagnostic imaging has a not negligible role because during the first intervention helps to have an idea of the possible location of the glands and thus to avoid the risk of recurrence and relapse due to ectopic or supernumerary tissue. (www.actabiomedica.it)

Key words: recurrent hyperparathyroidism; persistent hyperparathyroidism; subtotal parathyroidectomy; intraoperative parathyroid hormone measurement

Introduction

In secondary hyperparathyroidism all the parathyroid glands including supernumerary and ectopic, in relation to the altered calcium-phosphorus metabolism linked with chronic renal failure, undergo hyperplasia and increased production of parathyroid hormone (PTH) (1-3). This altered metabolism remains even after parathyroidectomy and can be associated with supernumerary or ectopic glands undetected under first intervention, residue parathyroid tissue left intentionally after subtotal parathyroidectomy or accidentally (seeding of glandular fragments within surgical breach after total parathyroidectomy), the forearm autograft (4). All procedures can cause secondary hyperparathyroidism...
 Secondary hyperparathyroidism is called “persistent” when there are high levels of serum calcium and parathyroid hormone within 6 months from the first cervical exploration, after this period a later occurrence of symptoms and signs of secondary hyperparathyroidism is called “recurrent” or “relapsed”. In persistent secondary hyperparathyroidism the residual tissue is widely secreting (adenoma, hyperplasia), while in the recurrent forms the interval is related to the progressive hyperplasia or adenomatous degeneration faced by the residual tissue. Proportionally the more residual glandular tissue is, the lower this period will be (5,6).

Severe untreated hyperparathyroidism may lead to various complications such as calciphylaxis(7-9), myelofibrosis (10), cardiovascular diseases and in some patients with longstanding secondary hyperparathyroidism after kidney transplant can cause tertiary hyperparathyroidism (11). At present surgery is the only effective therapeutic strategy for advanced renal hyperparathyroidism refractory to medical treatment.

Materials and methods

130 patients underwent subtotal parathyroidectomy for symptomatic secondary hyperparathyroidism. Among them, 4 cases experienced persistence and 9 relapse. The 4 patients with persistent hyperparathyroidism with dialysis average age of 9 years (range 1-18 aa) and postintervention levels of parathyroid hormone (PTH) > 350 ng/ml were subjected to reoperation after 6 months for the persistence of symptoms due to the finding of a supernumerary adenomatous gland in most cases sunk in the loose above thymic tissue not detected during the first operation. The 9 patients with recurrent hyperparathyroidism with dialysis average age of 7 years (range 1-13 aa) were subjected to reoperation, about 5 years after initial subtotal parathyroidectomy performed elsewhere, for the appearance of the typical symptoms (asthenia and itch), high levels of calcium (>10 mg/dl) and PTH (>400 ng/ml). At the reoperation were detected for 5 patients 2 more glands in over thymic position, while for the remaining patients it was found an hyperplasia of the residual glandular tissue perhaps left too abundant during the first intervention. Since 2003 we submitted 70 patients to subtotal parathyroidectomy taking advantage of the intraoperative dosage of PTH. Of such patients only 3 were subjected to reoperation 4 years after for the return of symptoms accompanied by a modest increase in PTH levels (PTH average 527 ng/ml) despite the abatement values in the post intervention was around 70% (mean baseline PTH 1128 ng/ml; I.O. PTH average 338 ng/ml) compared to baseline.

At the reoperation in one case it was found a supernumerary gland in above thymic position accessible with cervicotomy. In the other two cases there was an hyperplasia of the residue glandular tissue of the top right parathyroid left in the course of first intervention. In all cases we have performed a thorough diagnostic study with an ultrasound of the neck, cervical and mediastinal CT scan and finally parathyroid scintigraphy with dual tracer and for the last 3 cases also total body scintigraphy which allowed us to locate the glands in 100% of cases.

A classic cervicotomy was sufficient to remove the residual parathyroid in patients with persistent hyperparathyroidism. During the first surgery the strap muscles were separated along the median line, isolating later the thyroid lobes by blunt. In reoperation, opened the superficial fascial cutaneous plan, following the medial border of the sternocleidomastoid muscle, was identified the vascular nervous bundle which was slightly dislocated laterally to dissect then the strap muscles along the groove where adhesions with the thyroid capsule are generally minimal. Reached the esophageal plane it was reperted the recurrent laryngeal nerve with a cautious blunt dissection and once isolated it was loaded on elastic strip. Always following the medial border of the sternocleidomastoid muscle, was identified the vascular nervous bundle which was slightly dislocated laterally to dissect then the strap muscles along the groove where adhesions with the thyroid capsule are generally minimal. Reached the jugular dimple, it is possible to find the thymic tongue in which it was found the supernumerary gland, a gentle upward traction of the thymus on Duval’s clamp has enabled a better finding and resection of the included parathyroid. For cases of recurrent hyperparathyroidism it was enough a medial approach and sometimes lateral for the complete excision of the hyperplastic tissue.
Results

A total of 9 cases have showed recurrent hyperparathyroidism: 5 related to supernumerary above thymic glands for which it was enough a midline approach with complete exeresis of the hyperplastic tissue and the remaining 4 with residue hyperplastic glandular tissue for which it is performed the way of lateral approach described previously. The advent of the intraoperative technique of parathyroid hormone dosage allowed a better performance of the surgical technique for the last 3 patients undergoing reoperation. In the first case the 85% reduction of the levels of parathyroid hormone was obtained 10 minutes after the removal of the supernumerary gland (baseline PTH 560 ng/ml; I.O.PTH 84 ng/ml) while in the remaining 2 interventions the reduction of PTH was of 89% after 10 minutes of the removal of residue glandular tissue of the top right parathyroid. (mean baseline PTH 495 ng/ml; I.O. average PTH 55 ng/ml). After reoperation all patients had immediate regression of clinical symptoms with normalization of serum calcium and PTH levels.

Conclusions

Very often the real reason of the failure of parathyroidectomy is related to the incorrect preoperative anthropomorphological evaluation of the areas where there may be eventual hyperplastic glands. An excellent embryological knowledge of parathyroid glands is crucial to operative success during both initial and reoperative parathyroid surgical exploration.

The superior parathyroid glands are also known as parathyroid IVs, because they arise from the dorsal wing of the fourth pharyngeal pouch and from here migrate along the lateral thyroid sketch. Similarly, the inferior parathyroid glands are also known as parathyroid IIIs, because they arise from the dorsal part of the third pharyngeal pouch, and the thymus arises from the ventral part of the third pharyngeal pouch. As the inferior parathyroid glands and the thymus migrate together toward the mediastinum, they eventually separate. In most cases, the inferior parathyroid glands become localized near the inferior poles of the thyroid, and the thymus continues to migrate toward the mediastinum.

Anomalies during the migration process may involve variations in the number and location of the parathyroid glands, known as “parathyroid ectopias”. Arrest of thyroid descent can occur anywhere from the tongue down to the lower neck (12,13).

Each factor that can interfere with the embryological migration of parathyroid glands can determine the ectopic location.

This condition affects more frequently the inferior parathyroid glands, whose migration can stop at any point of the route from the angle of the mandible to the lower pole of the thyroid lobes. Moreover, if during the descent there is a close contact or an inclusion inside of the thymic sketch, the parathyroid can be dragged up in the anterior mediastinum, within or outside thymic location. According to the same mechanism, for the close relations in terms of development between thymic sketch and primitive heart, it may develop a rare parathyroid ectopia intrapericardial or intracardiac (14,15).

From these brief embryological premises, it is understood as, given the frequency and variability of ectopias, there is not a “normal” typical and precise allocation for parathyroid glands, especially for the lower, but we can speak rather of an “area” where they normally localize and of how often the boundaries between traditional and ectopic area tend to overlap, blending into one another until reaching the position frankly ectopic or the rare ectopia.

The wide range of parathyroid anatomic variations may make it difficult to predict a patient’s anatomy preoperatively. On the basis of these considerations, diagnostic imaging has a not negligible role because during the first intervention helps to have an idea of the possible location of the glands and thus to avoid the risk of recurrence and relapse due to ectopic or supernumerary tissue (16).

It was established that the reasons for failed surgery are due to unrecognized glands in 70% of cases, in 15% to ectopic glands, in 15% to supernumerary glands. In case of reoperation, moreover, it has proved indispensable intraoperative monitoring of PTH to evaluate the reduction or the persistence of high hormone levels (17-20) that require searching in all possibilities.
sible anatomical sites (even those ectopic): all that is meaningless without an accurate preoperative study that protects from a possible failure.

Finally, the reoperation can be avoided in more than 95% of cases as long as the surgeon has an excellent knowledge also of parathyroid glands embryology in the areas with higher rate of ectopy and above all operate a large and meticulous cervical exploration also to search possible supernumerary glands. For patients with relapsed or recurrent disease it is essential an accurate preoperative diagnostic study and the use of intraoperative parathyroid hormone measurement to guarantee total success (21,22).

References

1. Cunningham J, Locatelli F, Rodriguez M. Secondary Hyperparathyroidism: Pathogenesis, Disease Progression, and Therapeutic Options. Clin J Am Soc Nephrol 2011; 6: 913-921.
2. Fraser WD. Hyperparathyroidism. Lancet 2009; 374: 145-58.
3. Lappas D, Nourissios G, Anagnostis P, Adamidou F, Chatzigeorgiou A, Skandalakis P. Location, number and morphology of parathyroid glands: results from a large anatomical series. Anat Sci Int 2012; 87(3): 160-4.
4. Sakman G, Parsak CK, Balal M, et al. Outcomes of Total Parathyroidectomy with Autotransplantation versus Subtotal Parathyroidectomy with Routine Addition of Thymectomy to both Groups: Single Center Experience of Secondary Hyperparathyroidism. Balkan Med J 2014; 31:77-82.
5. Yumita S. Intervention for recurrent secondary hyperparathyroidism from a residual parathyroid gland. Nephrol Dial Transplant 2003; 18: 62-4.
6. Chou FF, Lee CH, Chen HY, Chen JB, Hsu KT, Sheen-Chen SM. Persistent and Recurrent Hyperparathyroidism After Total Parathyroidectomy With Autotransplantation. Annals Of Surgery 2002; 235(1): 99-104.
7. Lo Monte AI, Bellavia M, Damiano G, et al. A complex case of fatal calciphylaxis in a female patient with hyperparathyroidism secondary to end stage renal disease of graft and coexistence of haemolytic uremic syndrome. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2012; 156(3): 262-5.
8. Lo Monte AI, Bellavia M, Maione C, et al. Systemic calciphylaxis and thrombotic microangiopathy in a kidney transplant patient: two mixing fatal syndromes? Med Hypotheses 2012; 79(1): 74-5.
9. Gioviale MC, Damiano G, Lombardo C, Maione C, Buscemi G, Lo Monte AI. Bone resorption in kidney transplant recipients. Transplant Proc 2009; 41(4): 1170-4.
10. Bellavia M, Gioviale MC, Damiano G, et al. Is secondary hyperparathyroidism–related myelofibrosis a negative prognostic factor for kidney transplant outcome? Med Hypotheses. 2011; 77(4): 557-9.
11. Gioviale MC, Bellavia M, Damiano G, Lo Monte AI. Post-transplantation tertiary hyperparathyroidism. Ann Transplant 2012; 17(3): 111-9.
12. Gomes EM, Nunes RC, Lacativa PG, et al. Ectopic and extranumerary parathyroid glands location in patients with hyperparathyroidism secondary to end stage renal disease. Acta Cir Bras 2007; 22(2): 105-9.
13. Varga I, Pospisilova V, Gmitterova K, Galfova P, Polak S, Galbavy S. The phylogenesis and ontogenesis of the human pharyngeal region focused on the thymus, parathyroid, and thyroid glands. Neuro Endocrinol Lett 2008; 29(6): 837-45.
14. Nourissios G, Anagnostis P, Natsis K. Ectopic parathyroid glands and their anatomical, clinical and surgical implications. Exp Clin Endocrinol Diabetes 2012; 120(10): 604-10.
15. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. Am J Surg 2006; 191: 418-23.
16. Andrade JS, Mangussi-Gomes JP, Rocha LA, et al. Localization of ectopic and supernumerary parathyroid glands in patients with secondary and tertiary hyperparathyroidism: surgical description and correlation with preoperative ultrasonography and Tc99m-Sestamibi scintigraphy. Braz J Otorhinolaryngol 2014; 80(1): 29-34.
17. Pitt SC, Panneerselvan R, Chen H, Sippel RS. Secondary and tertiary hyperparathyroidism: the utility of ioPTH monitoring. World J Surg 2010; 34(6): 1343-9.
18. Clary BM, Garner SC, Leight GS Jr. Intraoperative parathyroid hormone monitoring during parathyroidectomy for secondary hyperparathyroidism. Surgery 1997; 122(6): 1034-8.
19. Gioviale MC, Gambino G, Maione C, et al. Use of monitoring intraoperative parathyroid hormone during parathyroidectomy in patients on waiting list for renal transplantation. Transplant Proc 2007; 39 (6): 1775-8.
20. Gioviale MC, Gambino G, Maione C, et al. Intraoperative parathyroid hormone monitoring during parathyroidectomy for hyperparathyroidism in waiting list and kidney transplant patients. Transplant Proc 2006; 38(4): 1003-5.
21. Rodriguez JM, Tsetelman S, Siperstein AE, et al. Localization procedures in patients with persistent or recurrent hyperparathyroidism. Arch Surg 1994; 129(8): 870-5.
22. Wells SA Jr, Debenedetti MK, Doherty GM. Recurrent or persistent hyperparathyroidism. J Bone Miner Res 2002; 17 (2):158-62.