

Surgical management of renal hyperparathyroidism: a preliminary series report

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Rezumat

Tratamentul chirurgical al hiperparatiroidismului renal: experiența preliminară

Introducere: Hiperparatiroidismul renal (HPR) este o complicație frecventă a bolnavilor cu insuficiență renală cronică supuși hemodializei și, în pofida multiplelor progrese ale tratamentului medical al acestei suferințe, paratiroidectomia este încă necesară în numeroase situații.

Pacienți și metodă: Este revăzută experiența proprie (prima în România) incluzând 43 observații de HPR operate în clinică între 1994-2009 fiind evaluate metodele diagnostice, indicațiile și tehnicile chirurgicale și rezultatele obținute în concordanță cu evoluția propriului nostru concept terapeutic. Seria noastră include 22 bărbați și 21 femei cu o medie de vârstă de 48 (limite 15-67) ani, supuși hemodializei (n=41) sau dializei peritoneale (n=2) de 7,7 (limite 3-13) ani. Trei pacienți au efectuat un transplant renal eșuat. Diagnosticul a fost stabilit prin anamneză, datele clinice (dureri osteoarticulare, osteoporoză, fracturi și deformări ale scheletului, astenie musculară, prurit sever, tulburări psihice), completate de valori anormale ale calcemiei, fosfatemiei, FA și PTH "intact". Ultrasonografia și scintigrafia paratiroidiană au obiectivat glandele "adenomizate" și leziunile tiroidiene coexistente.

Rezultate: Toți pacienții au fost operați practicându-se 24 paratiroidectomii subtotale și 19 paratiroidectomii totale (6 cu

autotransplant) din care două videoasistate. Morbiditatea postoperatorie a fost de 20,9 % (pareză recurențială și hemoragie postoperatorie câte un caz, hipocalcemie tranzitorie 3 cazuri, recidive 4 cazuri). Examenul histopatologic a relevat hiperplazie glandulară difuză (n=23) sau nodulară (n=19). Au mai fost identificate un carcinom paratiroidian (în a patra glandă), un timom și două microcarcinoame papilare tiroidiene. Controlul efectuat la 6-165 luni postoperator a consemnat vindecarea în 38 (79%) din cazuri.

Concluzii: Paratiroidectomia poate fi considerată o alternativă terapeutică cu efecte simptomatice evidente și de durată în HPR. Procedul operator trebuie individualizat, opțiunile pentru diferitele tehnici fiind încă discutate în literatură.

Cuvinte cheie: hiperparatiroidism renal, paratiroidectomie

Abstract

Background: Renal hyperparathyroidism (RHPT) is a frequent complication of uremic patients on hemodialysis and despite various advances in medical therapy parathyroidectomy is necessary in a semnificative number of cases.

Patients and methods: We reviewed our experience (first in Romania) regarding fortythree patients with RHPT operated on in our clinic between 1994 and 2009 evaluating the diagnosis methods, surgical indications, techniques and results together with the evolution of our own therapeutical concept. The study included 22 men and 21 women of median age of 48 (range 15-67) years, performing hemodialysis (n=41) or peritoneal dialysis (n=2) from 7,7 (range 3-13) years respectively. Three patients received an unsuccessful renal graft. The diagnosis was established by anamnesis, clinical complaints (mainly osteo-articular pains, osteoporosis, fractures and skeletal deformities,

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muscle weakness, severe itching and mental troubles), completed by abnormal values of calcemia, phosphatemia alkaline phosphatase and intact PTH. Ultrasonography and parathyroid scan were useful in “adenomised” parathyroids and coexistent thyroid pathology.

Results: All the patients were operated on. Twentyfour sub-total parathyroidectomies and 19 total parathyroidectomies (6 with autotransplantation), were performed (two video-assisted). There were no deaths and the operative morbidity was 20,9% (vocal cord hemiparesis and postoperative bleeding – each one case, mild transitory hypocalcemia three cases and recurrences four cases). Pathology revealed that RHPT was due to four gland diffuse hyperplasia (n=23) or nodular hyperplasia (n=19). One parathyroid carcinoma (in the fourth parathyroid gland), one thymoma and two papillary thyroid microcarcinoma was identified. Clinical and biochemical cure was achieved at median term control of 38 (range 6–165) months in 79,0% (n=34) of cases.

Conclusion: Parathyroidectomy is effective for long intervals as symptomatic therapy in cases of RHPT appearing in uremic patients on hemodialysis or after renal transplant but the optimal technique must be individualized on each case and still to be debated.

Key words: renal hyperparathyroidism, parathyroidectomy

Introduction

The association between chronic kidney disease (CKD) and the parathyroid glands (PT) was recorded more than a century ago by Mac Callum (1905) (1). Pappenheimer and Wilens observed the enlargement of PT glands in renal disease in 1935 and F. Albright and Reifstein defined in 1948 the concept of renal secondary hyperparathyroidism (RHPT) as “a condition where more parathyroid hormone is manufactured than is normal but where this hormone is needed for compensatory purpose” (2-5).

Some confusion appeared from the further description of “tertiary” hyperparathyroidism (THPT), term introduced by St Goar in 1963 to define an autonomous proliferation of PT glands in patients with prolonged evolution of secondary hyperparathyroidism (SHPT) on hemodialysis (6-7).

Actually both the secondary and tertiary HPT are considered as stages of the “same” renal osteodystrophy (ROD) although numerous authors enclosed in THPT only the patients which continue to have or develop hyperparathyroidism after a successful kidney transplantation (KT) (8-9).

In 2005 Kidney Disease: Improving Global Outcomes (KDIGO) sponsored a Controversies Conference in Madrid, Spain to reevaluate these definitions. The recommendations were that (1): the term ROD be use exclusively to define alterations in bone morphology associated with chronic renal disease (CKD) and (2): the term CKD – mineral bone disorder (CKD-MBD) can be used to describe the broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism as a result of CKD (10).

The nosographic appointment and the clear pathophysiological, biochemical and clinical boundaries between these two entities is not always easy to establish as well as the rate and durate of effectiveness of medical therapy in each case.

In early secondary form of HPT the stimuli for overproduction of parathyroid hormone (PTH) are multifactorial with no evident intrinsic parathyroid abnormality. Factors include hypocalcemia and deficient 1,25 dihydroxyvitamin D synthesis typically encountered in virtually all patients with dialysis dependent renal failure, to which added hyperphosphatemia and decreased expression of calcium and vitamin receptors and finally the consequent hypersecretion of PTH (9/12 12/13), all of them contributing to the hyperplastic growth of the PT glands (4,5,8,10).

Unresponsiveness at the adequate medical treatment in cases of SPTH or even after a KT combined with failure of suppression of the elevate levels of PTH lead to a progressive rising of the seric calcium concentration with propension of diffuse toward autonomous nodular hyperplasia of the PT glands and irreversible development of incapacitating and life threatening clinical manifestations defining better the hypercalcemic form of RPTH named tertiary HPT (5-7,10-12).

Therefore in a percentage of 0,7-14% the dialysis dependent patients required parathyroidectomy (PTx) for “severe” (refractory) RHPT. By the other side the reported requirement for PTx in cases of THPT is semnificatively smaller being estimated at 0,97-2,9% (11,13,14).

Patients and Methods

Between 1994 and 2009 43 consecutive patients (22 men, 21 women) with an average age of 48 (range 15-67) years old underwent surgery for “severe” RHPT at the IVth Surgical Clinic, “Gr.T. Popa” University of Medicine and Pharmacy Iași Romania. The accuracy of informations retrieved was verified by the operating surgeon (MRD).

Forty-one patients have been received long-term hemodialysis for a mean of 7,7 (range 3-13) years, two being treated with chronic ambulatory peritoneal dialysis from two and three years respectively. Chronic renal failure was produced by glomerulo(pyelo)nephritis in 31 cases, polycystic kidney disease in 4 cases, urolithiasis in 5 cases, in two cases by nephro-angiosclerosis and in one patient by diabetic nephropathy. Three cases have had a rejected KT performed 1-3 years earlier.

Even if the clear limits between secondary and tertiary HPT was not always easy to establish, we separed 23 cases with SPTH and 20 cases with THPT respectively.

All the patients were treated medically from variable periods with calcium supplementation, dietary PO₄ restriction, phosphate-binding agents and pulsed vitamin steroid products but the main symptoms as bone pain, weakness, pruritus, depression were getting progressively worse with calcium level and serum iPTH exceeding semnificatively normal values.

Clinical medical records, laboratory, localization imaging and other diagnosis data, operative notes, pathology reports and follow-up results were reviewed.

Results

All the patients was diagnosed and referred to us by consultant-nephrologists from different dialysis centers from all the country (Iasi, Oradea, Botoşani etc).

Clinical symptoms and signs constituted the main inclusion criteria of RHPT and are summarized in *Table 1*.

The assembly of clinical data is more important than the intensity of each of them and their consequences are more severe as those produced by CKD per se, affecting directly the quality and even the expectancy of life.

All the patients demonstrated biochemical criteria of RHPT and preoperative examination included serial examination of serum calcium, phosphorus and alkaline phosphatase concentration together with intact parathyroid hormone levels.

Routine determination of hormonal hematologic and renal function test were also done (*Table 2*).

Localization procedures. Ultrasonography (US) performed routinely and scintiscan were not reliable in our cases of RHPT since they do not correctly identify all pathologic glands and their utility resumed to detect 1-3 parathyroids larger then 5-10 mm or the coexistent thyroid lesions. (*Fig. 1. 2*)

Classic radiologic signs and BMB were only sporadic verified.

All the cases underwent cervical exploratory surgery. Our indications were framed on these recommended by K/DOQI and EDTA, but the decision in an individual case was only taken after the full consideration of the extent of his clinical problems in the presence of disabling complaints unresponsive to medical treatment and the long term prognosis and also the possibility of a renal transplantation. Therefore, surgery was resorted for those patients with clinical effects of RHPT including bone and joint pain the most important factor from the patient's point of view, severe untractable pruritus, muscle weakness and progression of soft tissue calcification. Also the surgical option was strengthened by the high level of intact PTH (up to 600 ng/l) and hypercalcemia or/and hyperphosphatemia and the presence of 1-3 enlarged PT glands at ultrasonography.

All patients underwent dialysis the day before intervention.

The operation was performed under general anesthesia.

The thyroid and parathyroid gland were exposed through a conventional collar incision with division and lateral retraction of the strap muscles. We isolated and ligated the middle thyroid veins and the thyroid lobes were alternatively turned over medially.

The exploration of the cervical anterior compartment was convinced according of the embryologic knowledge and surgical anatomy searching patiently the normal and common ectopic locations to identify all the PT glands.

In these years we performed all known surgical procedures in PTx for RHPT trying to adapt the technique to the form of the disease and especially to intraoperative founded lesions.

Initially and in majority of our patients (24 cases) we preferred subtotal PTx with removal of three glands and a "half" of the fourth one, depending on their size. The doubts arise from the homologation of the "least altered" PT gland and the viability and especially the adequate volume of the glandular tissue conserved. We also avow that in some patients we performed lesser procedures founding only three (three cases) or even two (one case) glands in spite of obstinate search, multiple frozen section or thyroid or thymic exeresis.

Only in six cases we carried out total parathyroidectomy with autotransplantation, attempting to excise all the glandular tissue (including the thymus in four situations) at surgery and also to chose the more adequate PT gland for autotransplantation. Fifteen-twenty pieces, sliced 1 to 3 mm were implanted into pockets prepared in the brahioradialis muscle of the forearm without arteriovenous fistula.

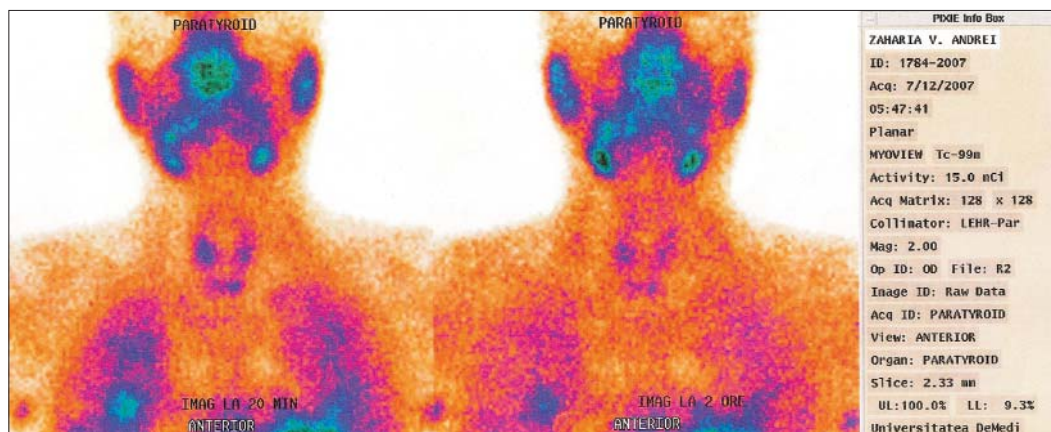
In the last period of time in 13 observation with long term evolving refractory RHPT with severe clinical syndrome, high levels of calcemia and iPTH and particularly intraoperative nodular aspect and huge volume (1-3 cm in diameter) of all the PT – therefore we have had practically any normal fragment of parenchyma to be preserved or grafted – our surgical approach was a total parathyroidectomy. (*Fig. 3*)

In spite of fear of adynamic bone disease we reconsidered this old procedure being practically "obliged" by the macroscopic aspect of all the PT glands.



Figure 1. Ultrasonography of the parathyroid glands

Figure 2. Parathyroid scintigraphy with ^{99}Tc tetrafosmin (four glands hyperplasia)



We also take into consideration the medical and social conditions of some patients who are not eligible for KT and condemned to effectuate hemodialysis indefinitely, hoping that the function of hyperplastic isolated microscopic clusters enhanced during the embryological development of the PT gland will assure suitable evolution.

Also a totalization of PTx was recently done in a young male patient (ZA, male 22 years old) which suffered elsewhere six months ago a “targeted” resection of only two glands and of course consecutive persistent HPT. At the reoperation two nodular, wide inferior PT glands were completely excised together with a fifth one situated retrosternally (it was our unique patient with an supranumerary gland).

A mean of 5,5 (range 0-10) frozen sections per patient were sent for pathologic probation. Checking the extemporaneous examination of intraoperative specimens surgical pathology reports of the removed parathyroid showed variable aspects suggesting the difference between SHPT and THPT. Therefore, in the 23 observations of SPTH, the PT were more or less homogenous sized with glandular tissue diffusely hyperplastic mostly with chief cell as predominantly cell type and occasionally oxyphyl cells (Fig. 4).

In the 20 cases of THPT the significantly larger but asymmetric volume and weight of the excised glands have had evidence of nodular hyperplasia with chief cells but with more oxyphyl and even clear cells. (Fig. 5) Occasionally one or two glands were greater (2 – 2,5 cm in diameter) than the others, this finding being considered the best evidence of PT autonomy. In one patient the pathologic examination discovered a parathyroid carcinoma.

This last peculiar case was C.V., male, 48 years old, with CKD on hemodialysis from 13 years with clinically (osteoarticular pains, muscle weakness, severe itching), biologically (Ca – 2,6 mmol/l, iPTH – 710 ng/l) diagnosed SHPT. Ultrasonography evidenced a left “thyroid nodule” of 3 cm in diameter. Intraoperatively three PT were discovered biopsied and excised but the fourth one was not found. A total lobisthmectomy for the “nodule” was performed and the frozen section was unclear but the definitive histological examination showed a parathyroid carcinoma (Fig. 6, 7). Postoperative after 4 ½ years the patient is well without recidive or metastasis con-

tinuing the hemodialysis.

The operation included also an exeresis of the thyroid gland, which in majority of the cases was intraoperatively decided. Subtotal thyroidectomies (n=1), lobisthmectomies (n=4), atypical resections (n=4), nodulectomies (2) or incidental biopsies (n=10), were performed for coexistent (multi)nodular goiter (discovering two incidental papillary microcarcinomas), suspected malignant lesions, or tactical purpose (two resected thyroid specimens containing intra-thyroidal parathyroid tissue).

The cervical excision of retromanubrial tissue including as much as possible of the thymic rests was not routinely done, being performed only in twenty cases of RHTP (in seven of them when one or two inferior PT were not found). Pathology revealed thymic tissue in five cases, benign thymoma and thymic cyst one case each, adipose tissue in 7

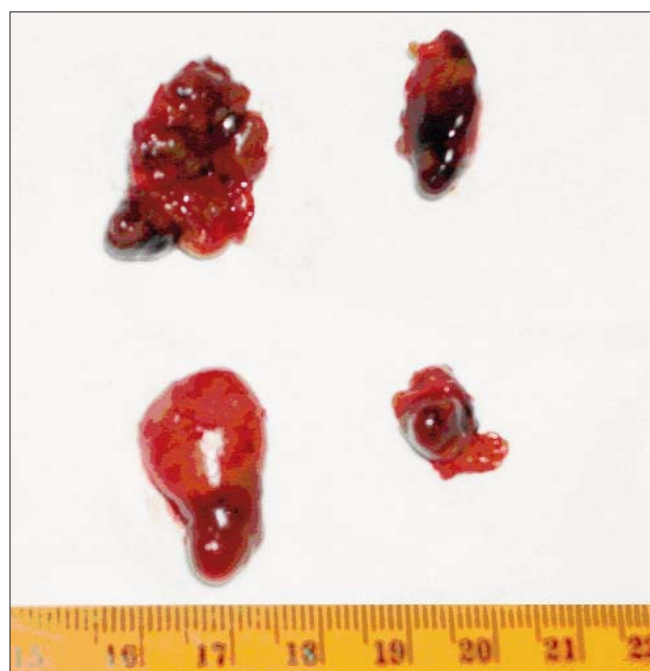


Figure 3. Operative specimen in a case of total parathyroidectomy

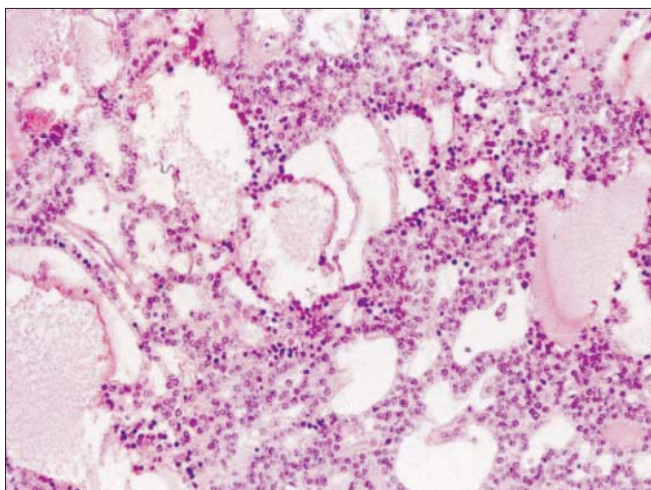


Figure 4. Diffuse chief cell hyperplasia

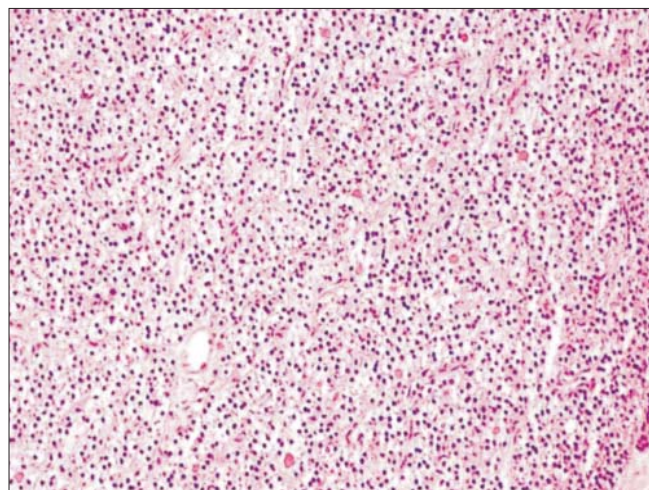


Figure 5. Nodular hyperplasia

cases and the missing PT in three cases (in one patient finding the fifth gland).

In our series there was no mortality related to the surgery and the postoperative complication rate was low: one post-surgical bleeding requiring evacuation, one laryngeal nerve injury and three patients with mild chemically apparent hypocalcemic symptoms resolving spontaneously as the remaining previously suppressed glandular tissues begin to function again or responded at oral calcium and vitamin D supplementation.

In two cases because of recurrence of hyperparathyroidism we must to remove fragments of the transplanted tissue in the forearm.

All the operated cases we followed and treated by the referring dialysis centers after discharge.

Of the 43 patients, 34 are still alive at follow-up ranged from 6 to 165 (mean 38) months after parathyroidectomy, two died at 13 and 24 months neglectful of their treatment and 7 cases were lost of observation.

Even if the monitorisation by each dialysis centers above mentioned was aleatory the overall clinical and biochemical response to surgery was satisfactory. Symptomatic improvement was reported in almost all the patients with early resolution of bone pain and itching while muscle weakness and nervous disturbances improved during a period of several months.

Preoperative hypercalcemia (in THPT patients), hyperphosphatemia and the increased alkaline phosphatase were normalised or improved in about three-quarters of patients. Serum iPTH also decreased in all the cases and in the majority of them the hormone's level maintained within the normal range.

Persistent HPT was evident in the four patients which has only two on three PT excised and in another two patients a recurrent graft dependent HPT was observed few months after removal of four glands and autografting imposing the excision of transplanted tissue under local anesthesia.

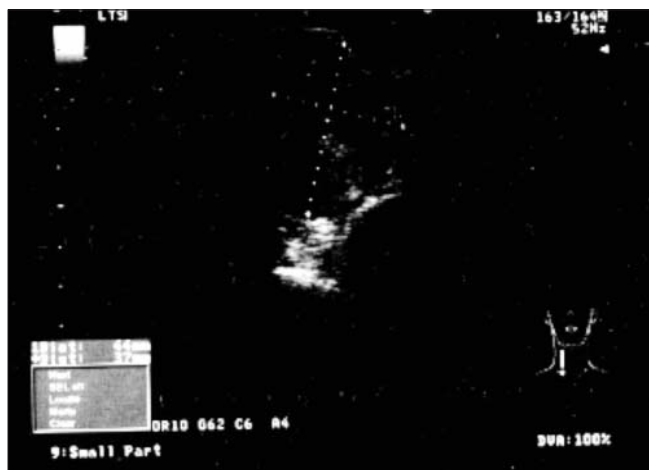


Figure 6. US of patient CV showing a left "thyroid nodule"

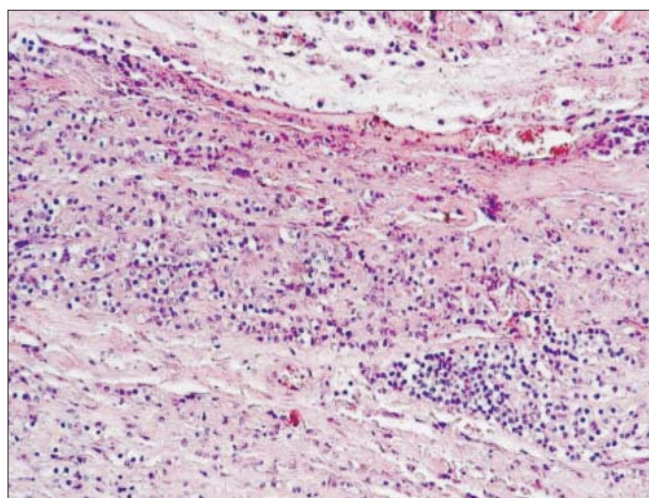


Figure 7. Parathyroid carcinoma

Discussions

Despite the better understanding of the pathogenic mechanism causing renal osteodystrophy and continuous improvements in medical management of this condition, the number of PTx among patients in whom the duration of dialysis exceed 10 years rise substantially to about 10 – 30 % annually (15).

On the other hand even if more than 8500 cases with end stage renal disease are treated with hemodialysis in numerous centers from our country it is a frustrating paucity of autochthonous studies about diagnosis and treatment of RHPT comparatively with abundant approach on this subject in international medical literature (16-19).

In this first Romanian retrospective work we try to review our preliminary experience in a series of patients with RHPT redefining the indication and presenting the feasibility, effectiveness and outcome of different performed surgical procedures.

Indifferent of the elusive limits between secondary and tertiary HPT the indications of surgery in patients with severe, refractory RHPT are obvious formulated in K/DOQI and EDTA guidelines, including as main criteria high levels of iPTH (above three times of normal values), hyperphosphatemia and/or persistent hypercalcemia and detection of enlarged PT glands by US (> 1 cm in diameter). In addition to these biochemical findings and assessments of parathyroid mass with US, is often failure of the pharmacologic therapy as a result of poor compliance during dialysis with progressive severe signs and symptoms: bone pain and arthralgia, skeletal deformities, fractures, incontrollable pruritus, neuromuscular and psychiatric manifestations, ectopic calcifications and calciphylaxia, anemia and also cardiovascular complications – hypertension, ischemic heart disease and heart failure (12,13, 20-22).

Several types of thought in the approach of these patients and different schools and authoritative specialists claimed worldwide their proper experience with comparable optimistic efficacy and low recurrence rates.

In 1960 Stanbury reported the first patient with complicated renal HPT undergoing successful “elective” subtotal PTx (23). Seven years later Ogg introduced total parathyroidectomy, but the procedure last for fear of challenging medical management in the long-term postoperative course (24). However this technique was reconsidered in the last decade by some surgeons including us with good results with regard to prevention to recurrence (25,26). Finally the total PTx with autotransplantation of glandular fragments into forearm muscle described by Wells remained increased popular with declining perception of graft failure or recurrent hyperparathyroidism (21,27,28,30).

Our thinking and decision in an individual case was framed in the international standards but surgery was performed only after the full consideration of the extent of the clinical problems and the presence of disabling complaints. In the whole judgment we also included anesthesia risks, presurgical and postsurgical complications, appreciation of short and long-term prognosis and last but not least the patients social

status and possibilities to receive a KT.

In our series we experienced all the techniques trying to adapt the approach at the patient’s above mentioned characteristics.

The larger number of subtotal PTx (and even some undesirable lesser procedures) which inaugurated our expertise formation, seduced us by its more physiological feature, appropriate operative time and reduced needs for prolonged postoperative medication. Nevertheless in the literature the risk of persistent/recurrent postsurgical HPT was recorded in 7-27% of patients submitted to this procedure and our own rate was 8,3% (2 cases).

In six cases we decided to use the TPTx with autotransplantation enthusiastically sustained by the Japanese school (21,23,28). Beside the length of operation time, the striking efforts to establish the less affected gland (in fact similar with this in previous technique), the good medium and long term results are affected by graft dependent recurrences (two cases in our experience) imposing the excision of probably wrong tailored glandular fragments.

Finally we resorted at the total PTx in 13 patients with “old” HPT and long period of hemodialysis, major clinical complaints, high values of calcemia and iPTH and especially symmetrical or not voluminous nodular glands without normal zones which “invited” to full extirpation (25,27). The classic policy of systematic frozen section seems undermined in these observations where macroscopic diagnosis is obvious.

The immediate and medium long results (until to five years) in these last cases are encouraging.

Remaning true to our philosophy in performing the more adapted operation in each case, the thyroid gland excisions were imposed by coexistent lesions or for tactical reasons while thymic exploration were more eclectic.

Our attempt to global evaluation of early and late postoperative results offered encouraging percentages of satisfactory results, according with the data reported in literature.

Surgical management provides metabolic benefits in patients with RHPT and its goals also prevent reverse or negative consequences on bone and cardiovascular systems.

The most appropriate operation for RHPT is still unresolved despite attempts to compare the efficacy of the different proposed procedures.

New therapies, minimally invasive surgery, direct injection of alcohol on a vitamin D derivative into the parathyroid gland under ultrasound guidance offers promising therapeutically perspectives.

In conclusion between allowing parathyroidectomy as gold standard therapy in selected cases of RHPT and a more skeptical “suboptimal” epithet of this procedure we think that in the actual stage of knowledge surgery yet remains a pragmatic method of treatment depending substantially on the surgeon’s preference and expertise. We hope also that new methods will help to perfect the treatment of this condition and its complications in CKD on dialysis and KT patients.

Further comparative studies and longer follow-up are mandatory to establish the best procedure or an alternative therapy.

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