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Research Article

Surgical approach and post-therapeutical effects of secondary hyperparathyroidism

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Abstract. Introduction: Hyperparathyroidism can be of three different types, each with its' corresponding causes: primary, secondary or tertiary. Secondary hyperparathyroidism is largely caused be hypocalcaemia of different etiologies, among which chronic kidney disease is the most frequent. Up to date, a surgical approach represents the only feasible treatment choice. However, opting for this procedure is a matter of controversy, given the numerous complications which can ensue. The object of this study is to analyze the efficacy of surgical treatment in patients with secondary hyperparathyroidism, on a lot of patients with CKD witch underwent surgical therapy Materials and Methods: 25 patients with secondary hyperparathyroidism due to chronic kidney disease were followed prospectively. All had undergone chronic dialysis, but had elevated parathormone (PTH) levels and symptoms due to hypercalcemia which constituted indications for surgical treatment. Results: Immediately following the procedure, a median calcium level of 17±266 pg/ml was obtained. Pre-surgical PTH values decreased with a mean of 93%. Pathological analysis confirmed glandular hyperplasia. Conclusions: The period over which patients benefited from haemodialysis does not influence PTH levels before surgery. Individual factors play an important role in the appearance of indications for a surgical treatment of hyperparathyroidism.

Key Words: secondary hyperparathyroidism, surgery, parathormone.

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Introduction

The main cause of secondary hyperparathyroidism is chronic kidney disease (CKD). The disruption of renal mechanisms determines a biochemical disbalance which acts as a systemic stimulus on the parathyroid glands. The action of the parathyroid hormone (PTH) is augmented in time, thus causing a further aggravation of an already existing disbalance. Avoidance of the etiologic factor can be achieved by functional kidney transplant, performed before the occurrence of structural parathyroid changes. This objective is difficult to reach nowadays, which is why the main course of action consists in removing the hyperplastic glands.

Surgical treatment represents the optimal choice, due to immediately favorable and sustained effects. The purpose is a decrease in the quantity of systemically stimulated parathyroid tissue, which entails a decrease in the continuous secretion of PTH. The current importance of this surgical approach is also prompted by the absence of a drug with long-term effectiveness, so that at least 1% of dialysis patients within one year and 15% within 10 years will eventually require parathyroidectomy (Li et al 2011). However, the decision of pursuing a surgical approach is a controversial one, due to associated complications. Lack of a consensus concerning the indication of each type of parathyroidectomy, compels the surgeon to make a decision based on personal experience (Busaidy et al 2012). The difficulty of the choice ensues from the fact that avoidance of recurrences as well as avoidance of permanent hypoparathyroidism is desired. Last but not least, the nephrologists' opinion needs to be taken into account, the approach of a uremic patient with secondary hyperparathyroidism being a multidisciplinary one. There are 3 types of hyperparathyroidism. Primary hyperparathyroidism develops due to hyperplasia or neoplasia of the parenchyma. Serum calcium levels are elevated or normal. Secondary hyperparathyroidism arises as an adaptive mechanism in the presence of CKD, largely triggered by hypocalcaemia (Busaidy et al 2012; Salusky et al 1999). Tertiary hyperparathyroidism implies an autonomic parathyroid hyperfunction in the context of secondary hyperparathyroidism (DeLellis 2010). Underlying the 3 aforementioned types are two major changes occurring in the glands: adenomatous proliferation and parathyroid hyperplasia. A differentiation of adenoma from hyperplasia cannot be done solely on histological criteria, an association with the surgical aspects being also necessary (Randoph&Urken 2010). The old criterion, based on the presence of a rim of normal tissue encapsulating the adenoma, is not always valid (Habener 1999). The 90:9:1 rule applies in the case of hyperparathyroidism: in 90% of cases, adenomas are identified, in 9%, hyperplasia and in under 1% parathyroid carcinoma is present (Smith&van Heerden 2007). Hyperplasia of chief cells can appear as an isolated entity or associated with familial primary hyperparathyroidism or multiple endocrine neoplasia syndromes (MEN). Hyperplasia does not occur in patients with MEN 2B or with thyroid medullary carcinoma. Glandular alterations can be viewed, initially, as a polyclonal hyperplasic process. Beginning here, under the

influence of mitotic errors or deficient DNA repair mechanisms, some patients may develop clonal lesions. Tumour genesis can therefore be viewed as a process during which, firstly, a genetic defect in the germinal line determines a multifocal pre-neoplastic proliferation with the secondary appearance of alterations leading to monoclonal proliferation (Smith&van Heerden 2007; Tominaga et al 1993; Fukuda et al 1993). Hyperplasia can affect the gland symmetrically or asymmetrically. Terminology encompasses classic hyperplasia, now called adenomatous hyperplasia and occult hyperplasia, referring to the cases in which a minimal increase in the size of the glands occurs (Potts et al 1999). This microscopic hyperplasia (60 mg) has no functional significance (Yoo&Young 2012). Chief cells, associated with transitional oncocytes or vacuolated chief cells can proliferate in a diffuse or a nodular pattern; they are arranged in a chord-like or follicle-like pattern, forming aggregates localized in the soft tissue of the neck or the mediastinum, defining parathyromatosis. The entity is responsible for the recurrence of the disease, appearing either post-surgically or ontogenetically. The quantity of stromal adipose tissue is significantly lower compared to normal tissue. If adipocytes are also prominently represented, the entity is called lipohyperplasia. Nodular hyperplastic glands can also present a "pseudo-rim" composed of normal tissue, similar to the one present in the case of adenomas (Åkerström&Juhlin 2010). A decrease in the expression of vitamin D receptors and an increase in cyclin D1 can be observed within the nodules, changes which cause aberrant regulation, hyper proliferation and resistance to drug therapies (Åkerström&Juhlin 2010; Inabnet et al 2009). Vacuolated chief cell hyperplasia is not associated with familial syndromes. It affects all of the four glands, conferring them a red-brownish color, with cysts and hemorrhage. The cells display numerous vacuoles and round, hyperchromatic nuclei (Sulková& Válek 2010), with lacunae and extensions resembling pseudopodia (Holick 1999).

Secondary hyperparathyroidism develops in the context of CKD, but can also arise with gastrointestinal malabsorption, vitamin D deficiency, hepatic disease (Habener et al 1999), malnourishment, vitamin D resistant rickets or hypermagnesemia (Holick 1999). The parathyroid gland's answer to hypocalcaemia is a sequential one and consists in an increase in PTH secretion concomitant with a decrease in intracellular degradation. Within hours, the stimulus becomes a chronic one and causes an increase in genic expression, which turns in time into chief cell proliferation and hyperplasia (Nussbaum et al 1999). Thus, if primary hyperparathyroidism is defined by an excessive PTH secretion, not correlated with serum calcium levels, secondary hyperparathyroidism represents an increase in the synthesis and secretion of PTH as a reaction to a persistent stimulus: hypocalcaemia (Brossard&D'Amour 2012). In the instance of CKD, all absorption mechanisms are deregulated. The events leading to hypocalcaemia are hyperphosphataemia, a decrease in calcium response to PTH and an abnormal vitamin D metabolism. Furthermore, this determines an increase in the numbers of PTH-producing cells, which are insensitive to the inhibitory effect of the hormone, thus secreting it continuously. In the context of CKD, changes in cell adenylate cyclase and reduction of calcitriol receptor levels can be observed. Early in the course of the disease, subnormal responses of calcium levels to PTH and bone resistance to the action of the hormone ensue. Incriminating causes are alterations in vitamin D metabolism, uremic toxins, phosphate retention, and alterations in PTH metabolism or PTH receptors (Yamada et al 2010). More specifically, normal functioning of the parathyroid glands is ensured by several receptors: calcium receptor, coupled with G protein, vitamin D receptors, a complex formed by the 1-c receptor for fibroblastic growth factor (FGF) and the Klotho coreceptor and an extracellular phosphate sensor. In the case of a glomerular filtration rate of under 90 ml/min, the increase in PTH or serum phosphate levels determines a release of FGF-23 from osteoblasts and osteocytes. FGF-23 levels constantly increase during the course of the kidney disease, maintaining phosphate homeostasis by inhibiting phosphate resorption in the proximal convoluted tubule, by reducing the activity of kidney 1-α-hydroxilase with a consequent decrease in circulating calcitriol and inhibition of PTH secretion. This inhibitory effect also manifests itself through an increase in 1-α-hydroxylase at the level of the parathyroid gland (Guideline Working Group 2008). Progressive reduction in nephron mass causes a decline in phosphate excretion ability and glands develop resistance to the action of FGF-23 by reduced receptor expression. The phosphate forms complexes with calcium, causing hypocalcaemia thus stimulating PTH synthesis also through a direct mechanism. Continuous increase in parathyroid mass leads to chronic hypercalcaemia with autonomous PTH secretion and a change in parathyroid set-point. These elements define tertiary hyperparathyroidism (Moore&Gawande 2007).

In vitro, parathyroid glands have the set-point (maximum level of PTH secretion halving) at a serum ionic calcium concentration of 1.03 mmol/L. In uremic patients however, the set-point is higher, so any increase in calcium concentration will lead to a decrease in PTH secretion (National Kidney Foundation K/DOQI 2003). In vivo, suppressing calcium levels are set between 10.5-11 mg/dL (Cozzolino et al 2004). The mechanism involved in up-grading the set-point is not yet known. Some hypotheses to be taken into consideration are changes in adenylate cyclase activity, gland hypertrophy through continuous secretion of small quantities of PTH, reduction of the number of calcitriol receptors with consequent decrease in the sensitivity of the glands (Norton&Sugg 1999). Bone changes represent the central element of the disease, the main ones involving mineralization and bone turn-over. The most common modification is osteitis fibrosa cystica, characterized by subperiosteal resorption, and it most frequently involves the fingers, the clavicle and the tibia. Osteoblastic and osteoclastic activity increases, thus increasing bone turn-over which determines a decrease in mechanical resistance. From a histological standpoint, bone marrow fibrosis, excess osteoid deposition and trabecular bone pattern can be observed (Norton&Sugg 1999; Gall et al 2010). The object of this study is to analyze the efficacy of surgical treatment in patients with secondary hyperparathyroidism, on a lot of patients with CKD witch underwent surgical therapy in Surgical Clinic I Cluj-Napoca.

Materials and Methods

The study population consists of 25 cases of hyperparathyroidism (12 men and 13 women) within the context of CKD and was followed prospectively. Mean age of women was 44±19 years. Men were aged 47±10 years. The patients were hospitalized in Surgical Clinic I Cluj-Napoca during the period of 2008 to

2012. The study was approved by University Ethics Committee. Patients were included in the study after they signed an inform consent form. All patients fulfilled the biochemical criteria of secondary hyperparathyroidism and were directed towards the surgical service of the clinic by their consulting nephrologist. The entire lot has benefited from continuous hemodialysis, including one patient who suffered a dysfunctional kidney transplant four years before parathyroid surgery. Indications for surgical intervention consisted of: PTH values greater than 500 pg/ml, hypercalcemia or hyperphosphatasemia and clinical manifestation of calciphylaxis, pathological fractures, bone pain, arthralgias and pruritus. All of the symptoms were unresponsive to pharmacotherapy. Follow-up at 6 months after the surgery was conducted on 6 patients.

All patients underwent a hemodialysis session 24-hours prior to the surgical intervention and PTH levels were brought to values raging from 947 to 3807 pg/ml, with a mean value of 2179±780 pg/mL. Subsequently, parathyroidectomy was performed under general anesthesia and with oro-tracheal intubation. Optimal exposure of the patients was achieved by placing them in dorsal decubitus, with raised shoulders and the neck being in extension. The surgeon maintained and ipsilateral position. Magnifying glasses were used. The procedure was considered optimal if PTH levels returned to the limits set as normal (<100 pg/ml). The group of suboptimal parathyroidectomy encompassed patients with PTH values between 100-300 pg/ml. Incomplete parathyroidectomy defined patients with PTH levels >300 pg/ml. Immediately after surgery, a minimum calcium level of 4 mg/l and a maximum of 969 pg/ml were obtained, with a median of 17±266 pg/mL.

All excised tissue was sent to the Pathology Department for histopathological diagnosis. In the case of excised pieces, which could not be classified as parathyroid glandular structure, an extemporaneous exam was performed. Macroscopically modified glands were characterized by size, hyperplasia type (nodular or diffuse), cellular pattern and degeneration type (cystic or calcification). Sections were cut and colored with haematoxylin-eosin. Results were expressed as mean±SD. Data were analyzed using the Epiinfo 7 software. We used Pearson correlation, Mann-Whitney test, and t-test for paired samples. The p values ≤ 0.05 were considered statistically significant.

Results and Discussions

Table 1 and Figure 1 depict clinical features and biochemical characteristics of the study population before surgery. All subjects presented bone pain that accentuated during the months preceding the surgery. Two of them had previous surgical interventions. The most prominent symptoms were: - pain in areas exploited mechanically: heels, knees. – muscle weakness. – accentuated pruritus associated with scratch marks. – metastatic calcifications taking the form of firm, not painful nodules, with juxtaarticular, subacromial and supraorbital localizations, at the angle of the mandible, in the subdeltoid bursa, on the distal radial epiphysis, the knee and in the abdominal soft tissue (Figure 1). Vascular damage, revealed during arterial Doppler examination, consisted in some cases of a bilateral diffuse calcium infiltration of distal arteries of lower limbs, with consequent necrosis of the fingers and necrotic leg ulcers. Other patients displayed diffuse vascular calcification, calcified atheromatosis at the

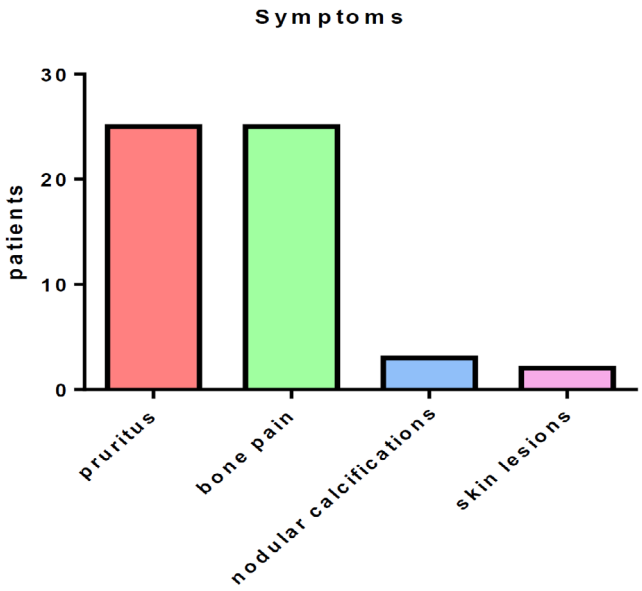

Figure 1. Patients' symptoms

Table 1. Patients' levels of PTH

PTH	<1000 pg/mL	1000 - 1500 pg/mL	1500 – 2000 pg/mL	2000 – 2500 pg/mL	2500 – 3000 pg/mL	3000 – 3500 pg/mL	>3500 pg/mL
Number of patients	1	3	10	3	4	3	1

level of the aorta, coronary arteries, iliac artery, at the emergence of the superior mesenteric artery and the renal arteries. The degree of bone damage was explored based on radiologic changes. The findings showed diffuse osteoporosis with damage to metacarpals and phalanges, damage to the small joints of the hands, osteolysis in the distal hand phalanges, bone cysts, degenerative changes in the acromioclavicular joint, coxarthrosis, peritrohanteritis, diffuse osteosclerotic changes of the spine and disc protrusion.

Statistical analysis of pre- and postsurgical values ascertained a highly statistically significant outcome: $p<0.001$. The difference between the two groups was 1892±799 pg/mL with a minimum of 879 pg/ml and a maximum of 3696 pg/ml. Pre-surgical values decreased with 93% with minimal and maximal values of 49%, respectively 100% (Figure 2).

Surgical treatment of secondary hyperparathyroidism includes the following variants: subtotal parathyroidectomy and total parathyroidectomy with or without autotransplantation. The surgical intervention is reported to have a 95% success rate compared to pharmacotherapy. Post-surgical complications however, raise a certain degree of doubt as to which the most effective way of reducing the size of hyperplastic tissue is. The prime role of this treatment is a decrease in PTH levels. Remaining tissue should be small enough that it isn't able to produce recurrences in the continuing presence of the systemic stimulus, yet big enough to avoid permanent hypoparathyroidism.

Immediately after the surgery, the decrease in calcium levels did not cause any emergencies. Treatment was initiated with 100 ml of calcium gluconate in 150 ml glucose 5% with an infusion rate of 20-30 ml. Serum calcium levels were obtained 4 hours after

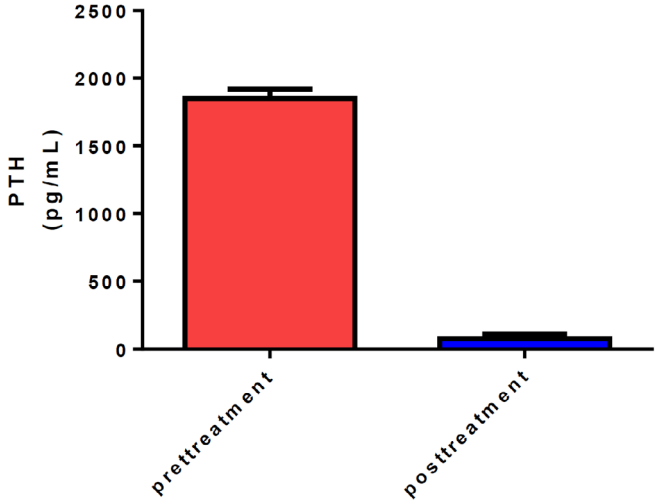

Figure 2. Patients' PTH level pre- and posttreatment

surgery. If their decrease exceeded 10%, 90 mg/h intravenous calcium was administered with subsequent monitoring every 6-12 hours. Total calcium values of <7.6 mg/dl (<0.95 mmol/L ionic calcium), between 7.6-8.4 mg/dl (0.95-1.05 mmol/l ionic calcium or >8.4 mg/dl (>1.05 mmol/l) represented indicators for adjusting intravenous calcium administration. The switch to oral calcium was done as soon as possible, accompanied by vitamin D intake. Also, the presence of hypomagnesaemia or hypophosphatemia was tracked. Long-term treatment consisted of calcium per os up to 4g/day, active vitamin D metabolite as alfacalcidol up to 4 µg/day, with continuous monitoring of serum calcium and magnesium levels.

Pathological changes were found within the glands: parenchyma consisting of diffuse or multinodular proliferations with normal cells, without atypias and decreased adipose tissue. Chief cells, oxyphil cells and clear cells formed a trabecular, follicular or solid pattern. Nodules were framed by conjunctive tissue. Variable degrees of haematic infiltration, hemosiderin deposits and vascular stasis were observed (Figures 3A+3B). The pieces not confirmed to be parathyroid glands were represented by: thyroid nodules (4 cases), lymph nodes with sinusal hystiocytosis and stasis (2 cases) and fibro-adipose tissue (1 case).

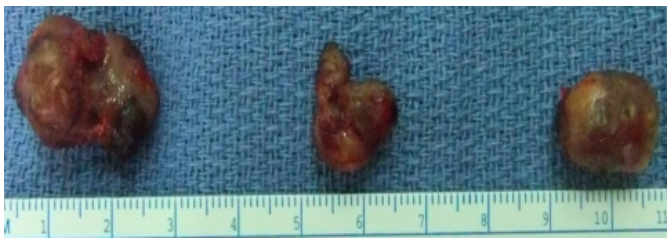

Figure 3A. Excised parathyroid glands – macroscopy

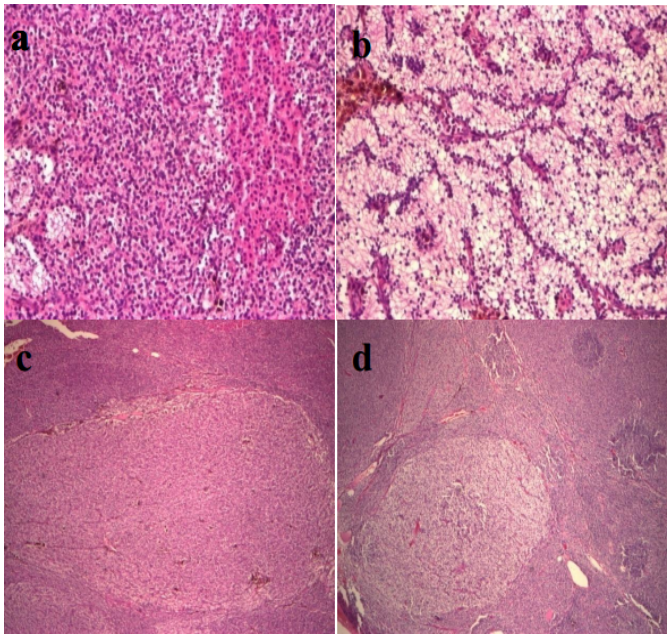

Figure 3B. Histology images showing pathological changes of parathyroid glands: a) Chief cell hyperplasia (magnification 4x).b) Clear cell hyperplasia (magnification 20x). c) Nodular hyperplasia (magnification 4x).d) Mixed hyperplasia (magnification10x)

Conclusions

The leading challenge for the surgeon in the approach of a uremic patient with secondary hyperparathyroidism is represented by the avoidance of a recurrence, associated with subtotal parathyroidectomy. Total, suboptimal or incomplete parathyroidectomy poses a risk through the possible presence of supernumerary or ectopic glands, in which case the main objective is not attained. The most important side effect is represented by permanent hypoparathyroidism. This is why subtotal or total parathyroidectomy accompanied by autotransplantation are preferred. Secondary hyperparathyroidism following CKD has been registered predominantly among female patients of young age, compared to male patients. PTH values most prominently represented before surgery are situated between 1500-2000 pg/ml. These values reflect the delay of the surgical treatment and the reluctance of the patient facing this therapeutic alternative. The necessity for surgical intervention arises at a mean of 12 years from the onset of CKD (which corresponds to the dialysis period). However, there are cases in which a period of 29 years passed until parathyroidectomy was called for. Still, no correlation has been found between the length of the evolution of the disease and PTH levels before surgery. Overall, this illustrates the influence of individual factors and the variability in the development and progression of the disease.

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