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Normocalcemia and Persistent Elevated Serum Concentrations of 1-84 Parathyroid Hormone after Operation for Sporadic Parathyroid Adenoma: Evidence of Increased Morbidity from Cardiovascular Disease

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Abstract. Elevated serum concentrations of 1-84 parathyroid hormone (PTH) after operation for sporadic parathyroid adenoma have been reported in previous studies, years after operation for primary hyperparathyroidism (pHPT). The cause and significance of this finding have not been elucidated. Primary hyperparathyroidism was diagnosed in 195 patients from January 1987 to December 1998. Operation for pHPT was performed in 124 patients. To evaluate long-term effects of elevated serum 1-84 PTH, biochemical variables and pre- and postoperative diseases were investigated from hospital case records. Of the 124 patients operated on, 103 had a solitary adenoma. Among these patients, 60 had normal serum concentrations of 1-84 PTH and calcium postoperatively, 38 patients had follow-up for more than 12 months (range 12–207 months—group A). Persistent elevated serum concentrations of 1-84 PTH and normocalcemia were found in 23 patients. Fourteen patients had follow-up for more than 12 months (range 15–76 months—group B). Two patients had persistent pHPT, and 18 were normocalcemic, but in this retrospective study data on serum 1-84 PTH were not available. No significant differences were found between groups A and B at the time of diagnosis concerning clinical characteristics. More that 12 months after operation for pHPT, the patients in group B, with persistent elevated serum concentrations of 1-84 PTH, had a significantly ($\chi^2 = 11$, $p = 0.005$, and power of test 0.66) higher frequency of cardiovascular diseases from ischemic heart disease and hypertension. Persistent elevated serum concentrations of 1-84 PTH after operation for sporadic parathyroid adenoma may be associated with development of cardiovascular disease. This group of patients therefore needs lifelong control and, possibly, medical intervention.

Transient or persistent inappropriate increases in serum 1-84 parathyroid hormone (PTH) concentration after surgery for pPTH have been reported in previous publications [1–4]. Frequencies between 4% and 40% have been observed. Possible explanations for postoperative increased serum PTH concentrations in the presence of normocalcemia have been reduced bone mass or changes in the calcium-sensing receptors in the remaining glands causing an increased set-point of PTH secretion [4]; postoperative serum calcium in the lower normal range [5], or reduced renal function and increased age [1, 3].

From longitudinal studies of patients with mild primary hyperparathyroidism (pHPT), it has been shown that survival was significantly lower among hypercalcemic patients than among control subjects, mainly because of cardiovascular diseases [6]. Untreated pHPT or hypercalcemia is a risk factor for premature death from left ventricular hypertrophy [7]. After successful operation for pHPT, left ventricular hypertrophy is reversible, particularly in normotensive patients [7]. In the same study, 5 of 123 patients had persistent elevated serum PTH concentrations but normocalcemia 41 month after operation. These patients did not show any significant reduction of myocardial hypertrophy.

The aim of the present study was to evaluate the possible impact on cardiovascular morbidity of persistent elevated serum concentrations of 1-84 PTH after operation for sporadic parathyroid adenoma.

Subjects and Methods

Using hospital case records, patients diagnosed with pHPT from January 1987 to December 1998 were studied retrospectively. Two biochemical variables, 1-84 serum PTH (normal range 10 to 50 ng/L) and serum ionized calcium (normal range 1.15 to 1.35 mmol/L) were investigated, as were any preoperative or postoperative diseases. Patients with a family history of pHPT, multiple endocrine neoplasia syndrome, or renal impairment were excluded from the study. Primary hyperparathyroidism was diagnosed in 195 patients. Twenty-four patients were treated with alcohol injection into a single parathyroid adenoma, 47 patients were untreated in the study period, and 124 patients underwent operation for pHPT. Of the 124 patients operated on, 103 had a solitary adenoma (Fig. 1). From this group, 60 patients had normal postoperative serum concentrations of 1-84 PTH and calcium immediately or within few months. Of these 60 patients, 38 patients (mean age, 54 years; range, 22 to 74 years) had follow-up for more than 12 months (range 12 to 207 months) and were designated group A. In 23 patients, persistent elevated serum concentrations of 1-84 PTH and normocalcemia were found in the early postoperative phase. Fourteen of these patients (mean age, 58 years; range, 37 to 76 years) had follow-up for more than 12

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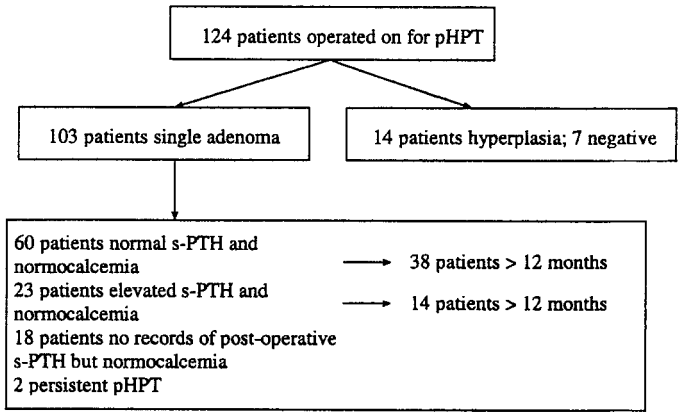

Fig. 1. Of the 124 patients operated on for primary hyperparathyroidism (pHPT), 103 had a solitary adenoma. From this group, 60 patients had normal postoperative serum (s) concentrations of 1-84 PTH and calcium immediately or within few months. Of these, 38 patients had follow-up for more than 12 months (range 12–207 months, group A). In 23 patients, persistent elevated serum concentrations of 1-84 PTH and normocalcemia were found in the early postoperative phase. Fourteen of these patients had follow-up for more than 12 months (range 15–76 months, group B). Two patients had persistent pHPT, and 18 were normocalcemic, but in this retrospective study we do not have data for serum 1-84 PTH.

months (range, 15 to 76 months) and were designated group B. Two patients had persistent pHPT, and 18 were normocalcemic but in this retrospective study we do not have data for serum 1-84 PTH.

The definitions of congestive heart failure and angina pectoris or myocardial infarction were based on the "Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines" and intention to treat.

Statistical Analysis

Data are expressed as mean values ± SEM. Statistical comparisons were performed using the nonparametric Mann-Whitney test and chi-squared test. A two-tailed p-value less than 0.05 was considered significant. The power of the tests was calculated as described elsewhere [8]. Data analyses were carried out with the SPSS programs (SPSS Inc., Chicago, IL, USA).

Results

There were no significant differences between the patients in group A and group B as regards mean age (54 years; range 22 to 74 years in group A vs. 58 years; range 37 to 76 years in group B), mean preoperative serum 1-84 PTH concentrations (164 ± 19 ng/L in group A vs. 252 ± 98 ng/L in group B), preoperative and postoperative mean ionized serum calcium concentrations (preoperative 1.60 ± 0.02 mmol/L vs. 1.65 ± 0.06 mmol/L; postoperative 1.28 ± 0.01 mmol/L vs. 1.26 ± 0.02 mmol/L, in groups A and B, respectively). The frequency of postoperative cardiovascular disease in the whole group of patients (n = 60) with normal serum 1-84 PTH (32 ± 2 ng/L) and ionized calcium concentrations was significantly lower when compared with the group of patients (n = 23) with persistent elevated serum 1-84 PTH (76 ± 6 ng/L) but normocalcemia (χ^2 = 17, p = 0.002, and power of test 0.81) (Table 1). More than 12 months postoperatively, the patients in group B (n = 14), with persistent elevated serum 1-84 PTH, had a significantly (χ^2 = 11, p = 0.005, and power of test 0.66) higher frequency of cardiovascular disease from ischemic heart disease and hypertension when compared with group A (n = 38).

Table 1. Cardiovascular disease in patients followed up after operation for pHPT, with postoperative normalization of serum calcium.

	Hypertension	CHF	MI	AP
Postoperative (within 1 year)*				
Normal s-PTH (n = 60)	1			
Elevated s-PTH (n = 23)	1	1	2	3
Postoperative (> 12 months)**				
Normal s-PTH (n = 38)	1			
Elevated s-PTH (n = 14)	1		2	2

CHF: congestive heart failure; MI: myocardial infarction; AP: angina pectoris; s: serum; pHPT: primary hyperthyroidism; PTH: 1-84 parathyroid hormone.
*χ^2 = 17, p = 0.002; **χ^2 = 11, p = 0.005.

Postoperative serum 1-84 PTH concentrations correlated positively to serum 1-84 PTH concentrations at the time of diagnosis (p = 0.02) and negatively to postoperative serum ionized calcium concentrations (p = 0.04) in both groups A and B (multiple regression analysis: r = 0.4, p = 0.02). Extending the calculations to the whole group of patients with normal (n = 60) and elevated (n = 23) postoperative serum 1-84 PTH concentrations, similar results were found (p = 0.01 and p = 0.002, respectively; multiple regression analysis: r = 0.49, p = 0.0001).

Discussion

Patients with pHPT have increased mortality from cardiovascular diseases [6, 9]. The increased risk of premature death persists even after successful surgery, although that risk decreases gradually with time [9, 10]. The association between premature death from cardiovascular disease and pHPT may result from left ventricular hypertrophy [7, 10–12]. However, after successful operation for pHPT, left ventricular hypertrophy is reversible [7, 13], except in the case of persistent elevated serum 1-84 PTH concentrations but normocalcemia after operation for pHPT, in which left ventricular hypertrophy apparently is not reversible [7].

We found that the frequency of cardiovascular disease in patients undergoing operation for pHPT was significantly higher in those with normocalcemia and elevated serum 1-84 PTH concentrations than in the with normal postoperative serum 1-84 PTH and calcium concentrations (Table 1). Extending the observation period to more than 12 months, patients with persistent elevated serum 1-84 PTH still had a significantly higher frequency of cardiovascular disease from ischemic heart disease and hypertension (Table 1). Even if the absolute number of patients with cardiovascular disease was small, the difference was highly significant by chi-square test (χ^2 = 11), and with a high power of the test (0.66).

In our study, no differences were found in postoperative serum ionized calcium concentrations between groups A and B. Previous studies have dealt with cardiovascular disease in nonoperated patients with pHPT or successfully operated patients with normal postoperative serum 1-84 PTH and calcium concentrations. To our knowledge, the present data are the first published indicating a relationship between increased levels of 1-84 PTH and cardio-

vascular morbidity. Previous papers have, however, pointed to this possibility. Thus Stefenelli et al. [7] showed that patients with postoperative persistent elevated serum 1-84 PTH concentrations but normocalcemia had irreversible left ventricular hypertrophy, and Symons et al. [11] found an increased serum concentration of 1-84 PTH and normal serum calcium in 5 of 8 patients with hypertrophic cardiomyopathy, whereas left ventricular hypertrophy did not occur in any of 6 patients with hypercalcemia alone. This relation suggests that 1-84 PTH per se, and not a rise in extracellular calcium concentration, might be implicated in left ventricular hypertrophy. The possible individual contributions of increased 1-84 PTH and ionized calcium to cardiac abnormalities in patients with pHPT remain unresolved. Elevated 1-84 PTH and calcium both exert a hypertrophic effect on cardiomyocytes [14], whereas 1-84 PTH induces cellular calcium influx independent of serum calcium concentration [15, 16]. Combining these observations with the present study and previous studies, it seems that elevated 1-84 PTH concentration may contribute to postoperative cardiovascular disease in a subgroup of these patients.

In the present study we found persistent elevated serum 1-84 PTH concentrations but normocalcemia in 12% of patients operated on for pHPT, which is lower than some studies [1, 2] but comparable to others [3, 5, 7]. Inappropriate elevated serum 1-84 PTH concentration has been explained by impaired renal function in both short- and long-term studies [1, 3, 5], as well as to "hungry bones" [1]. In the present study and other studies [2, 7] none of the patients suffered from obvious renal impairment as judged from serum creatinine concentrations. This might not reflect the glomerular filtration rate, but in our study all patients with or without persistent 1-84 PTH elevation had normal serum creatinine. Moreover, "hungry bones" is thought to be a transient condition and is an unlikely cause of increased serum 1-84 PTH years after successful parathyroidadenomectomy. Changes in the calcium-sensing receptor in the remaining normal parathyroid glands might, however, explain the inappropriate elevated serum 1-84 PTH concentrations. Because these glands are exposed to high 1-84 PTH and calcium concentrations for years, changes in the calcium-sensing receptor expression may account for the increase in the set-point of 1-84 PTH secretion [17, 18].

In conclusion, persistent elevated serum concentrations of 1-84 PTH after operation for sporadic parathyroid adenoma, may be associated with an increased risk of cardiovascular disease. This group of patients therefore needs lifelong control and, possibly, medical intervention. We suggest that large multicenter studies of pHPT should pay close attention to the risk of premature death from cardiovascular disease in this group of patients.

Résumé. Plusieurs publications ont déjà fait état de la persistance de concentrations sériques élevées en 1-84 parathormone (PTH) après intervention pour adénome parathyroïdienne sporadique, parfois des années après l'opération initiale pour hyperparathyroïdie primitive (pHPT). La cause et la signification de ce phénomène n'ont pas encore été élucidées. Parmi 195 patients chez lesquels on a fait le diagnostic d'hyperparathyroïdie primitive entre jan 1987 et déc 1998, 124 ont été opérés. Grâce aux dossiers hospitaliers, les variables biochimiques et la morbidité pré et postopératoire ont été analysés pour évaluer les effets à long terme de l'élévation persistant de la PTH. Parmi les 124 patients opérés, 103 avaient un adénome solitaire dont 60 avaient des concentrations sériques postopératoires normales, en PTH comme en calcium. 38 patients ont été suivis plus de 12 mois (extrêmes 12–207 mois (group A). Chez 23 patients, on a trouvé des concentrations de PTH seriques élevées persistanttes alors que ces patients étaient normocalcémiques. Quatorze patients ont été suivis pendant plus de 12 mois, extrêmes 15–76 mois (groupe B). Deux patients avaient une pHPT persistante et 18 étaient normocalcémiques mais dans cette étude rétrospective, toutes les données en ce qui concerne la PTH sérique n'étaient pas disponibles. On n'a trouvé aucune différence significative entre les groupes A et B au moment du diagnostic en ce qui concerne les caractéristiques cliniques. A plus de 12 mois après opération pour pHPT, les patients dans le groupe B avec une concentration de PTH sérique élevée persistante avaient significativement (χ^2 = 11, p = 0.005, et puissance du test 0.66) plus de pathologie cardiovasculaire en rapport avec une cardiopathie ischémique et l'hypertension. La persistance de concentrations sériquese élevées de PTH 1-84 après opération pour adénome sporadique de la parathyroïde pourrait être associée au développement de maladie cardiovasculaire. Ce groupe de patients demande donc une surveillance à vie et parfois une intervention chirurgicale.

Resumen. En estudios previos se constató que años después de una intervención quirúrgica por hipeparatiroidismo primario (pHPT) provocado por adenomas esporádicos de paratiroides, persistían concentraciones séricas elevadas de la 1-84 hormona paratiroidea (PTH). Su etiología y significación todavía no se ha dilucidado. Entre enero de 1987 ydiciembre de 1998, 195 pacientes fueron diagnosticados de hiperparatiroidismo primario, operándose 124. Merced a las historias clínicas, parámetros bioquímicos pre y postoperatorios se investigaron los efectos tardíos de la elevación sérica de la PTH. De los 124 pacientes intervenidos, 103 presentaban un adenoma solitario. De ellos, 60 mostraron valores séricos postoperatorios normales tanto de PTH como del calcio; 38 pacientes con un seguimiento superior a 12 meses (rango 12–207 meses) constituyeron el denominado grupo A. En 23 pacientes se registraron concentraciones séricas elevadas de PTH con normoclacemia; 14 pacientes con seguimientos superiores a los 12 meses (rango 15–76 meses) constituyeron el grupo B. Dos pacientes presentaron un pHPT recidivante; 18 eran normocalcémicos pero las cifras retrospectivas de PTH no se pudieron encontrarse en la búsqueda retrospectiva. No se observaron diferencias significativas por lo que al diagnóstico y características clínicas se refiere entre los pacientes del grupo A y B. Transcurridos más de 12 meses desde la operación por pHPT, en los pacientes del grupo B, con persistencia de concentraciones séricas elevadas de PTH, se desarrollaron con más frecuencia (χ^2 = 11, p = 0.005, poder del test 0.66) enfermedades cardiovasculares debidas a isquemia cardiaca e hipertensión. El mantenimiento de concentraciones séricas elevadas de la 1-84 hormona paratiroidea tras la operación por adenoma esporádico de paratiroides provoca el desarrollo de enfermedades cardiovasculares. Este grupo de pacientes requiere un seguimiento de control a lo largo de toda su vida y posiblemente, un tratamiento médico.

References

1. Duh Q-Y, Arnaud CD, Levin KE, et al. Parathyroid hormone: before and after parathyroidectomy. Surgery 1986;100:1021–1030
2. Irvin GL, Newell DJ, Morgan SD. Parathyroid metabolism after operative treatment of hypercalcemic (primary) hyperparathyroidism. Surgery 1987;102:898–902
3. Bergenfelz A, Valdemarsson S, Tibblin S. Persistent elevated serum levels of intact parathyroid hormone after operation for sporadic parathyroid adenoma: evidence of detrimental effects of severe parathyroid disease. Surgery 1996;119:624–633
4. Mimura Y, Kanauchi H, Ogawa T, et al. Inappropriate elevation of intact PTH in the presence of normocalcemia after successful surgery for primary hyperparathyroidism. Endocr. J. 1998;45:609–616
5. Lundgren E, Rasted J, Ridefelt P, et al. Long-term effects of parathyroid operation on serum calcium and parathyroid hormone values in sporadic primary hyperparathyroidism. Surgery 1992;112:1123–1129
6. Ljunghall S, Jakobssson S, Joborn C, et al. Longitudinal studies of mild primary hyperparathyroidism. J Bone Miner. Res. 1991;6(Suppl 2):S111–S116
7. Stefenelli T, Abela C, Frank H, et al. Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up. J. Clin. Endocrinol. Metab. 1997;82:106–112

8. Altman DG. Practical Statistics for Medical Research. London. Chapman & Hall, 1991:455–460
9. Hedbäck G, Oden A, Tisell LE. The influence of surgery on the risk of death in patients with hyperparathyroidism. World J. Surg. 1991; 15:399–405
10. Hedbäck G, Odén A. Increased risk of death from primary hyperparathyroidism: an update. Eur. J. Clin. Invest. 1998;28:271–276
11. Symons C, Fortune F, Greenbaum RA, et al. Cardiac hypertrophy, hypertrophic cardiomyopathy, and hyperparathyroidism—an association. Br. Heart J. 1985;54:539–542
12. Lind L, Skarfors E, Berglund L, et al. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J. Clin. Epidemiol. 1997;50:967–973
13. Piovesan A, Molineri N, Casasso F, et al. Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidism. Clin. Endocrinol. 1999;50:321–328
14. Schluter KD, Weber M, Piper HM. Parathyroid hormone induces protein kinase C but not adenylate cyclase in adult cardiomyocytes and regulates cyclic AMP levels via protein kinase C-dependent phosphodiesterase activity. Biochem. J. 1995;310:439–444
15. Palmieri GM, Nutting DF, Bhattacharya SK, et al. Parathyroid ablation in dystrophic hamsters. Effects on Ca content and histology of heart, diaphragm, and rectus femoris. J. Clin. Invest. 1981;68:646–654
16. Zhang YB, Smogorzewski M, Ni Z, et al. Altered cytosolic calcium homeostasis in rat cardiac myocytes in CRF. Kidney Int. 1994;45: 1113–1119
17. Kifor O, Moore FD, Wang P, et al. Reduced immunostaining for the extracellular Ca^{2+}-sensing receptor in primary and uremic secondary hyperparathyroidism. J. Clin. Endocrinol. Metab. 1996;81:1598–1606
18. Gogusev J, Duchambon P, Hory B, et al. Depressed expression of calcium receptor in parathyroid gland tissue of patients with hyperparathyroidism. Kidney Int. 1997;51:328–336