

Association between primary hyperparathyroidism and thyroid disease.

Role of preoperative PTH



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BACKGROUND: *The association between patients with surgically treatable thyroid disease and patients affected by PHPT is not just accidental.*

MATERIALS: *We report 591 patients who underwent total thyroidectomy in our center. Data, collected during the preoperative period according to our protocol for candidates to total thyroidectomy, included: type of thyroid disease, sex, age, type of surgical procedure, preoperative PTH and plasmatic calcium level. Calcium plasmatic level has been monitored at 24 hours after surgery, on day 6 and monthly for 6 months.*

RESULTS: *On 591 cases, PTH above the normal range were present in 19.1% (113 patients), all asymptomatic for PHPT. 30 were males (26.6%) and 83 females (73.4%), with a mean age of 62.97 ± 12.51 years and 57.38 ± 15.09 years ($p=0.19$). The mean preoperative PTH and calcium plasmatic level were 104.4 ± 21.96 pg/ml and 119.7 ± 37.93 pg/ml ($p=0.39$) and 9.21 ± 0.59 mg/dL e 9.37 ± 0.87 mg/dL ($p=0.45$) respectively. Intraoperative exploration proved a pathological parathyroid gland in 12 on 113 cases. In 9 of the 12 patients with parathyroid adenoma, hypocalcaemia developed. It resolved in 7 days for 4 patients and within 30 days for the others. No hypocalcaemia has been recorded at a 6 months follow up for the 97 considered (4 were lost at follow up).*

CONCLUSION: *Preoperative PTH measurement for all patients undergoing total thyroidectomy may offer a concrete tool to screen and identify the above-described category of patients, with no additional cost for further radiological investigations, because this class of patients will be submitted to bilateral cervical exploration associated with a total thyroidectomy.*

KEY WORDS: Hypocalcaemia Primary hyperparathyroidism, PTH, Thyroidectomy.

The role of surgery for patients affected by asymptomatic primary hyperparathyroidism has not been established yet. Since the 70's, when screening tests have been introduced, the incidence of hyperparathyroidism has increased.

The association between patients with surgically treatable thyroid disease and patients affected by PHPT is not

just accidental and multiple reports about this association are present in literature ¹⁻⁴.

In 1990 the consensus Conference about the treatment of asymptomatic PHPT identified the criteria that indicated surgery: Calcium plasmatic level of 1-1.6 mg/dL, 24 h urinary calcium >400 mg, creatinine clearance reduced by 30%, bone mineral density z-score <2.0 (for-cam), age <50 years. In 2002 those criteria have been reviewed as follows: calcium plasmatic level (above upper limit of normal) 1,0 mg/dl, 24 h urinary calcium >400 mg, creatinine clearance reduced by 30%, bone mineral density t-score <2,5 at any site, age <50 years (Table I) ⁵. According to these guidelines, to recent articles and also to the different indications to the surgical approached guided by clinical findings, we reviewed prospectively our

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TABLE I - Guidelines 1990 versus guidelines 2002 for parathyroid surgery in asymptomatic primary hyperparathyroidism

	1990	2002
Serum calcium (above upper limit of normal)	1-1.6 mg/dl	1.0 mg/dl
Bone mineral density at any site	z-score <-2.0 (forearm)	t-score<-2.5
24 h urinary calcium	>400 mg	=
Creatinine clearance	reduced by 30%	=
Age (years)	<50	=

series of patients who underwent surgery for thyroid disease to evaluate the association between thyroid and parathyroid in surgical patients.

Materials and methods

We report 591 patients who underwent total thyroidectomy in our center in the period January 2006 and June 2008. Exclusion criteria were: recurrence of goiter after surgery, medullary or anaplastic carcinoma of the thyroid, chronic renal failure, previous parathyroid surgery or clinically evident PHPT, patients with ongoing hormonal or calcium based therapy.

Data, collected during the preoperative period according to our protocol for candidates to total thyroidectomy, included: type of thyroid disease, sex, age, type of surgical procedure, preoperative PTH and plasmatic calcium level.

Calcium plasmatic level has been monitored at 24 hours after surgery, on day 6 and monthly for 6 months.

Statistical analysis has been performed using Kyplot 5.0 (KyensLab Inc.©.) Student T-test has been used to compare variables, values of $p < 0.05$ have been considered significant.

Results

On 591 cases, PTH above the normal range were present in 19.1% (113 patients), all asymptomatic for PHPT.

TABLE II - Preoperative laboratoristic parameters protocol in patients candidates to total thyroidectomy

Evaluation of:
SERUM CALCIUM
PTH
TSH, FT4
CALCITONIN
THYREOGLOBULIN

Table III - Clinical cases: 113 cases on 591 patients thyroidectomized

	Male (30 pts)	Female (83 pts)	P
Mean age(years)	62.97 ± 12.51	57.38 ± 15.09	0.19
PTH (pg/ml)	104.4 ± 21.96	119.7 ± 37.93	0.39
Serum calcium (mg/dl)	9.21 ± 0.59	9.37 ± 0.87	0.45

Table IV - Elevated PTH and thyroid diseases related

56/113	goiter	49.6%
13/113	hyperfunction	11.5%
3/113	Basedow disease	2.6%
41/113	DTC*	36.3%

* Differentiated thyroid cancer

Of these 113, 30 were males (26.6%) and 83 females (73.4%), with a mean age of 62.97 ± 12.51 years and 57.38 ± 15.09 years ($p=0.19$) respectively. The mean preoperative PTH and calcium plasmatic level were 104.4 ± 21.96 pg/ml and 119.7 ± 37.93 pg/ml ($p=0.39$) (Normal values 12-72 pg/ml) and 9.21 ± 0.59 mg/dL e 9.37 ± 0.87 mg/dl ($p=0.45$) respectively (normal values 8.5 – 10.5 mg/dL) (Table III).

Indications to surgery in patients with abnormal PTH were: euthyroid goiter 56 (49.6%), hyper functioning goiter in 13 patients (11.5%), Basedow-Graves disease in 3 (2.6%), thyroid neoplasm, in 41 cases (36.3%) (Table IV). In 6 cases preoperative ultrasound suggested a parathyroid adenoma together with thyroid disease. No further investigations have been performed since bilateral cervical exploration was mandatory anyway in all patients undergoing total thyroidectomy.

Intraoperative exploration proved a pathological parathyroid gland in 12 on 113 cases. No ectopic adenoma was detected.

In 101 of the remaining cases, transient postoperative hypocalcaemia has been recorded in 63 patients (62.3%) at 24 hours after surgery (mean calcium levels 7.58 ± 0.18 mg/dL). In all cases symptoms resolved within 7 days. In 9 of the 12 patients with parathyroid adenoma, hypocalcaemia developed. It resolved in 7 days for 4 patients and within 30 days for the others. No hypocalcaemia has been recorded at a 6 months follow up for the 97 considered (4 were lost at follow up).

Discussion

The association between thyroid and parathyroid disease has been described in patients affected by non-functioning pathology or in the absence of previous preoperative radiation therapy.

Up to date, the extent of the real association between the 2 populations compared to the normal population is still unclear and it is dependent on the preoperative work up of patients undergoing surgery for diseases involving one of the 2 endocrine entities.

When the patient is affected by parathyroid disease, cervical ultrasound and scintigraphy may help identifying thyroid problems, while if the patient has a known thyroid disease, cervical ultrasound alone, without a systematic measurement of preoperative PTH, may underestimate the extent of a coexistent parathyroid pathology^{6,7}.

We have previously reported¹ a 13.1% incidence of elevated preoperative PTH in patients candidates to total thyroidectomy. In the same study, of the 19 patients, asymptomatic for PHPT but with elevated PTH values, investigated preoperatively with cervical ultrasound and sesta mibi scintigraphy, 15 had intraoperative confirmation of parathyroid adenoma while 4 had evidence of hyperplasia.

In 2002⁵ a systematic review on guidelines for the treatment of hyperparathyroidism the value of calcium plasmatic level indication surgery for parathyroid surgery has been shifted from 1-1.6 mg/dl to 1.0 mg/dl. Surgery was also indicated for patients who refused long term medical follow up.

Endocrine surgery has evolved in recent years and many mini-invasive techniques have been proposed. These improvements changed not only the technical approach to endocrine surgery but also the indications to it, especially regarding surgery of the cervical area⁸⁻¹³.

A recent article reporting a survey among endocrinologists in Switzerland showed that in the large majority of cases (72%) the guidelines adopted for patients with asymptomatic PHPT are those from 2002.¹⁴ Mini invasive approaches encouraged doctors to a more liberal behaviour towards surgery.

Another article¹⁵ reported the clinical course of surgically treated and untreated symptomatic PHPT in a 15 years follow up period. It is to be noted that in this study asymptomatic patients showed a progression of the disease in 37% of cases. This, together with the relatively recent update of the treatment guidelines of PHPT, has to focus on the role of long term medical follow up and of the risk/benefit ratio.

Zanocco and Sturgeon in 2008¹⁶ presented a study reviewing their series in the light of 2002 guidelines focusing on 2 major issues: 1) surgery as the only definitive treatment for PHPT, 2) the age of patients affected asymptomatic PHPT (> or < 50 years). Previous series had proved the benefit in terms of quality of life after parathyroidectomy in asymptomatic patients younger than 50 years old, proving this approach to be cost effective also in patients who would be outside the indications suggested in the NIH consensus conference guidelines for PHPT. Cost analysis demonstrated that long term medical follow up, compared to the cost of a one

time surgical procedure, is in favour of surgery for patients aged 50 or less, suggesting this is the most cost effective treatment for younger patients affected by asymptomatic PHPT.

Lowe et al.¹⁷ identified in his series a group of asymptomatic patients with normal calcium plasmatic level but elevated preoperative PTH that in the 18.9% of cases, after a mean follow up of 3.1 years, demonstrated to develop hypercalcemia, suggesting elevated PTH may be an early presentation of PHPT.

In our series we observed a group of patients with a similar clinical behavior, that has been identified after the introduction of preoperative PTH screening in all patients candidates to total thyroidectomy.

The answer to which approach is the most suitable for this category of patients can be partially found in the study from Ambrogini et al.¹⁸ where a surgical procedure has been chosen with a significantly better outcome in terms of general wellness, vitality, social life and BMD. The Authors suggest the results of their study support the role of surgery, intended as parathyroidectomy, also for patients with mild PHPT, outside NIH criteria. Clinical presentation of early PHPT is likely to differ from the overt form of the disease; in the initial phase neuropsychiatric manifestations can be present even in the beginning, defining a subclinical scenario.

In our series, no differences in terms of age, sex and plasmatic calcium level have been reported among the patients with elevated preoperative PTH. During bilateral cervical exploration, in 12 cases a parathyroid adenoma and no case of multiglandular parathyroid disease have been identified. None of the patients was preoperatively symptomatic for PHPT.

Preoperative PTH measurement for all patients undergoing total thyroidectomy may offer a concrete tool to screen and identify the above-described category of patients, with no additional cost for further radiological investigations, because this class of patients will be submitted to bilateral cervical exploration associated with a total thyroidectomy.

Riassunto

SCOPO DELLO STUDIO: L'associazione tra pazienti con patologia tiroidea da trattare chirurgicamente e pazienti affetti da iperparatiroidismo primitivo (PHPT)

MATERIALI E METODI: Abbiamo prospetticamente analizzato 591 pazienti sottoposti presso il nostro reparto ad intervento di tiroidectomia. I dati raccolti nella fase preoperatoria in accordo al protocollo di studio applicato a questi casi includevano: il tipo di patologia tiroidea, il sesso, l'età, il tipo di procedura chirurgica, il dosaggio del PTH preoperatorio, il livello plasmatico di calcio. Tale dato è stato inoltre rilevato anche dopo 24 ore dall'intervento chirurgico, in 6° giornata e nei sei mesi successivi.

RISULTATI: Su 591 casi, abbiamo registrato valori di PTH al di sopra della norma in 19,1% dei casi (113 pazienti), tutti asintomatici per HPHT.30 erano maschi (26.6%) e 83 femmine (73.4%) con una età media pari a 62.97 ± 12.51 anni e 57.38 ± 15.09 anni ($p=0.19$). Il valore medio di PTH preoperatorio e di calcio plasmatico era pari a 104.4 ± 21.96 pg/mL e 119.7 ± 37.93 pg/ml ($p=0.39$), 9.21 ± 0.59 mg/dL e 9.37 ± 0.87 mg/dl ($p=0.45$) rispettivamente. L'esplorazione intraoperatoria bilaterale ha evidenziato la presenza di ghiandola patologica paratiroidea in 12 su 113 casi. In 9 di questi pazienti si è registrato lo sviluppo di ipocalcemia postoperatoria che si è risolta in 7 giorni per 4 casi e entro 30 giorni negli altri. Nessun caso di ipocalcemia si è registrato a 6 mesi nei 97 pazienti con PTH preoperatorio elevato che abbiamo seguito al follow up (4 persi al follow up).

CONCLUSIONE: La misurazione del PTH preoperatorio in tutti i pazienti con indicazione alla tiroidectomia offre un concreto ausilio nella identificazione dei pazienti affetti anche da iperparatiroidismo senza la necessità di ulteriori esami diagnostici radiologici, poiché questo gruppo di pazienti sarà comunque sottoposto ad intervento di esplorazione cervicale bilaterale.

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