CLINICAL STUDY

Retrospective analysis of the association of nodular goiter with primary and secondary hyperparathyroidism

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Abstract

Background: The association of hyperparathyroidism (HPT) with thyroid disease has long been known, but the mechanisms underlying such an association have not yet been clarified.

Objective: To elucidate the main factors determining this combination of endocrine diseases, in a retrospective multicenter study.

Methods: We retrospectively reviewed all patients referred for parathyroid scintigraphy in the period 1990–1999. A total of 487 patients in the age range 17–65 years were selected for the analysis (339 women and 148 men); group A included 241 patients with primary and group B 246 patients with secondary HPT.

Results: A total of 124/241 patients in group A (51.5%), but only 92/246 patients in group B (38.2%) had thyroid disorders (notably nodular goiter) associated with HPT ($P = 0.0035$). Thyroid disorders were evenly distributed throughout the entire 17–65 years age range in group A, but 17–40-year-old patients in group B had significantly fewer thyroid disorders than the older patients of the same group (15.5% compared with 43.3%, $P < 0.002$), as expected in a general population. In patients with primary HPT there was no difference in the prevalence of thyroid disease between women and men, whereas the ratio of women to men in secondary HPT patients with thyroid disease was about 3:1.

Conclusions: These results demonstrate an increased prevalence of nodular goiter in patients with primary rather than secondary HPT, and are consistent with a possible role of increased endogenous calcium concentrations (a hallmark of primary, but not of secondary, HPT) as a goitrogenic factor in patients with HPT.

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Introduction

The frequent association of nodular goiter with primary hyperparathyroidism (HPT) has been reported since the early 1950s (1), the prevalence of this thyroid disorder being retrospectively reported in an average 38.1% of hyperparathyroid patients (median 37.5%), although ranging widely between 22 and 70% (1–13). It should be noted that, despite a quite high prevalence of nodular goiter in patients with primary HPT (54% as based solely on visible or palpable thyroid disease), Lever *et al.* (8) concluded that this prevalence was not significantly greater than that observed in their autopsy-based control group (46.4%).

Although no definite conclusion has as yet been drawn on the factor(s) causing this association, it

should be noted that early experimental data obtained in the mouse indicate some goitrogenic activity of calcium (14); a possible link to thyroid nodular goiter can therefore be found in the increased serum calcium concentrations that have long been considered a characteristic feature of primary HPT. Nevertheless, an increased prevalence of thyroid disorders has also been reported in uremic patients with secondary HPT; however, these observations involved relatively small groups of patients (15, 16).

In a different clinical setting, a common iatrogenic factor such as prior external irradiation of the head and neck region (17–20) might have some involvement in the combined occurrence of non-medullary differentiated thyroid cancer and parathyroid adenomas (21–30).

It should be noted that association of thyroid with parathyroid disorders has also been confirmed in retrospective and prospective studies conducted with a reverse approach: when patients with thyroid disease were screened for HPT, this latter condition was found to reach up to tenfold and more of the prevalence expected in the general population (31–35).

It should also be pointed out that, in the majority of the reports mentioned above, the frequent association of thyroid disorders with HPT has mainly been focussed on the primary rather than the secondary form, whereas the association has not extensively been analyzed for patients stratified according to primary or secondary HPT. Primary, secondary, tertiary and ectopic HPT are all characterized by increased concentrations of parathyroid hormone (PTH), altered calcium–phosphate balance and similar clinical patterns, at least as far as bone involvement is concerned. However, whereas increased serum calcium concentrations are frequently found in patients with primary, tertiary and ectopic HPT, patients with the secondary form most frequently exhibit low serum concentrations of calcium.

Therefore, primary and secondary HPT provide, in humans, a spontaneous model in which the hypothesis that calcium is a goitrogenic factor can be tested. On the basis of this rationale, we retrospectively evaluated the prevalence of thyroid disorders (notably nodular goiter) in a large group of patients with either primary or secondary HPT. The design of this retrospective study was based on information which was systematically available concerning specifically the prevalence of nodular goiter. It should be noted that the prevalence of thyroid dysfunction not associated with nodular goiter (not the main focus of the analysis) was possibly underestimated, as information on subtle abnormalities of thyroid function or autoimmunity was not similarly available on a systematic basis in the population under study.

Patients and methods

The present study was based on the retrospective analysis of the clinical records of all patients consecutively referred for parathyroid scintigraphy to eight Italian Nuclear Medicine Centers in the period 1990–1999. Only patients in whom either primary or secondary HPT was confirmed and whose clinical records included detailed information on the thyroid status (with particular attention to nodular goiter) were considered for the analysis. Particular attention in the selection of patients was also paid to the following exclusion criteria: (i) patients living in a known area of endemic goiter; (ii) patients with the multiple endocrine neoplasm syndrome, and (iii) patients younger than 17 years or older than 65 years; these age limits were adopted because HPT is very rare in the younger

patients, whereas the prevalence of nodular goiter increases spontaneously with age.

A total of 487 patients (339 women and 148 men) met all criteria for inclusion in the analysis. There were 241 patients with primary (group A) and 246 patients with secondary HPT (group B). All cases of secondary HPT were linked to end-stage renal failure, with patients in the pre-dialysis phase (about 20%), undergoing dialysis treatment (about 55%), or post-transplantation (about 25% of the patients). Of the 135 patients undergoing long-term dialysis treatment, 123 (91%) were maintained on chronic hemodialysis and 12 (9%) were maintained on continuous ambulatory peritoneal dialysis. The ratio of women to men was 190:51 in group A and 143:103 in group B.

Considering groups A and B together, 82 patients were in the age range 17–40 years (49 women and 33 men; average age 31.2 years), and 405 patients were in the age range 41–65 years (290 women and 115 men; average age 56.4 years). Mean ages of patients with primary or secondary HPT were nearly identical (52.8 years compared with 51.7 years respectively). Likewise, in primary and secondary HPT, the mean ages of the corresponding subgroups of patients in the younger age range (17–40 years) and in the older age range (41–65 years) were nearly identical: 31.9 years compared with 31.0 years and 56.6 years compared with 56.3 years respectively.

A history of prior neck irradiation during the peripubertal age was ascertained in 41/487 patients (8.4%). All but two of these patients were older than 40 years at the time of parathyroid scintigraphy; patients with prior neck irradiation were nearly equally distributed between the primary and secondary HPT groups: 19/241 (7.9%) and 22/246 (8.9%) respectively. None of the patients with prior neck irradiation had thyroid or parathyroid cancer.

Diagnosis of HPT was based on clinical history (including signs, symptoms, or both, of bone disease), blood chemistry (including PTH assays), urine analysis (calciuria), ultrasonography and parathyroid scintigraphy. The latter examination was performed with either the dual tracer technique (^{201}Tl -chloride and $^{99\text{m}}\text{Tc}$ -pertechnetate) (36, 37) or the dual phase technique based on the cathionic lipophilic tracer $^{99\text{m}}\text{Tc}$ -sestamibi (38–40). Assay of the serum concentrations of PTH was performed by radioimmunoassay or immunoradiometric methods identifying the intact hormone; the upper normal limits of such assays ranged between 12 and 80 pg/ml, depending on the different techniques utilized in the different centers participating in this study. Confirmation of HPT on the basis of surgery or cytology (ultrasound-guided fine-needle aspiration), or both, was available in more than 70% of the patients. Concerning primary HPT in particular, diagnosis of the condition was not systematically linked to frankly increased serum calcium concentrations, as previously reported also by others (33, 41).

The identification of nodular goiter was based on information that was systematically available for all patients: clinical history, physical examination, ultrasonography and thyroid scintigraphy, with the baseline thyroid hormonal profile (serum thyroid-stimulating hormone and free thyroid hormone concentrations) being routinely requested in case of positive identification of nodular goiter. Conversely, no further testing (such as the thyrotropin-releasing hormone test and thyroid autoimmunity pattern) was systematically available in case of minor thyroid dysfunctions not associated with nodular goiter.

Statistical analysis

Significance of the differences between groups for variables with a Gaussian-type distribution (such as the serum calcium concentrations) was evaluated by the two-tailed Student's *t*-test for unpaired data. For variables with a non-Gaussian distribution (such as the serum PTH concentrations), statistical analysis was performed after ANOVA transformation.

In order to test the working hypothesis that the two groups of patients (A and B, respectively with primary and with secondary HPT) are characterized by different prevalence of coexisting thyroid disorder(s) associated with HPT, we considered the difference between the two prevalence values. The level of significance of this difference was assessed by the *z* test of normal distribution for comparison of proportions (42), and the corresponding *P* value (probability of similar response in the entire population) was computed. Because the direction of the difference was not known in advance, two-tailed statistical testing was used.

Confidence intervals were also evaluated, as parameters for assessing inferences about estimated differences between groups, these inferences often being those associated with hypothesis testing, *P* value and, among other factors, sample size.

Results

Despite some overlapping values between the two groups, patients with primary HPT (group A) had average serum calcium concentrations about 26% greater ($P < 0.0001$) than those in patients with secondary HPT (group B): 2.76 ± 0.31 mmol/l (median 2.74 mmol) compared with 2.19 ± 0.36 mmol/l (median 2.35 mmol/l).

Definite overlapping between groups A and B was also observed for the serum PTH concentrations, notwithstanding that the average values were much greater in patients with secondary than in patients with primary HPT ($P = 0.0002$ for the subgroup of patients in whom serum PTH was measured with an assay method with an upper normal limit of 40 pg/ml; $P < 0.0001$ for all other subgroups). As a matter of fact, when the values obtained with different assay

methods were considered separately, the average ratios between serum PTH concentrations in patients with secondary and those with primary HPT ranged between 2.74 and 6.50 (mean value 4.95) in the various groups for each assay method (data not shown).

In line with previous reports, the prevalence of thyroid disorders observed in the entire population of patients with HPT was quite high: 220/487 (45.2%) of the patients (161 women and 59 men). Apart from the finding of three patients with papillary thyroid cancer (two with primary and one with secondary HPT; none with previous neck irradiation), the vast majority of thyroid disorders proved to be euthyroid nodular goiter (210 patients, 75% with isolated thyroid nodules), and seven patients had hyperfunctioning goiter (five cases of single toxic adenoma).

When the patients were divided according to primary or secondary HPT (groups A and B respectively) the prevalence of thyroid disease was found to be 124/241 in group A (51.5% of the patients, 100 women and 24 men), which was significantly greater ($P = 0.0035$) than the 96/246 prevalence in group B (39.02% of the patients, 61 women and 35 men) (Fig. 1). Serum PTH concentrations in patients with primary HPT with nodular goiter did not significantly differ from those without nodular goiter.

There was no significant difference in the prevalence of nodular goiter between patients in group A in the age range 17–40 years (18/37; 48.7%) and those in the 41–65 years age range (106/204; 52%). Furthermore, in this group the proportion of patients with nodular goiter remained quite constant at about $50 \pm 2\%$ for different age ranges throughout the 17–65-year age range. In contrast, the older patients in group B had a significantly greater prevalence of thyroid disease (89/201; 44.3%) than the younger patients in the same group (7/45; 15.6%, $P < 0.002$). Conversely, in both age ranges (17–40 years and 41–65 years) for both primary and secondary HPT there was no significant difference in the mean age of patients with or without coexistent thyroid disease: 34 years compared with 30 years in the younger primary HPT subgroup; 53 years compared with 55 years in the older primary HPT subgroup; 31 years compared with 30 years in the younger secondary HPT subgroup; 53 years compared with 54 years in the older secondary HPT subgroup.

When sex distribution was taken into account, the prevalence of nodular goiter remained significantly greater in the women in group A (100/190; 52.6%) than in those in group B (59/143; 41.3%, $P = 0.04$, confidence interval 0.5 to 22.1%) (Fig. 2). In contrast, although the prevalence of thyroid disease was similarly greater in the men in group A (24/51; 47.1%) than in those in group B (35/103; 34%) (Fig. 2), this difference did not reach statistical significance ($P = 0.1$, confidence interval 2.6 to

Figure 1 Incidence of coexisting thyroid disease in HPT, in the entire group of patients (above) and in groups having the primary or the secondary form (below). with t.d., with coexisting thyroid disease; w/o t.d., without coexisting thyroid disease.

28.7%), probably because of the smaller statistical sample under analysis.

Finally, comparing the ratio of women to men among patients with thyroid disease in group A (0.52) with that of patients with thyroid disease in group B (0.75), one can conclude that the probability of developing thyroid disease is virtually identical for female as for male patients with primary HPT (0.52), whereas it is much greater for female than for male patients with secondary HPT (0.75, as expected in the general population).

Discussion

The main findings of the present statistical analysis based on a large sample population with either primary or secondary HPT can be outlined as follows: (i) the prevalence of coexisting thyroid disease in patients with HPT is greater than expected in the general population; (ii) the prevalence of coexisting thyroid disease (notably euthyroid nodular goiter) is significantly greater in primary than in secondary HPT; (iii) the greater prevalence of coexisting thyroid

Figure 2 Incidence of coexisting thyroid disease in patients with primary or secondary hyperparathyroidism, according to sex. with t.d., with coexisting thyroid disease; w/o t.d., without coexisting thyroid disease.

disease in patients with primary HPT is independent of the influence of sex, age, and serum PTH concentrations (these last are actually greater in secondary than in primary HPT); (iv) the effect of sex and age on coexisting thyroid disease in patients with secondary HPT mirrors the pattern observed in the general population (although with a somewhat increased prevalence).

As to the first point, the results of our retrospective analysis suggest that the prevalence of coexisting euthyroid nodular goiter in patients with HPT (an overall 45.2% irrespective of primary or secondary HPT) is greater than the value expected in the general adult population. In this regard, the prevalence of goiter in a geographical area with an average mild iodine deficiency, such as the mixed Italian regions involved in the present analysis, is expected to range between 5–19% (43, 44), or even lower according to other estimates (4–10%) (45).

Concerning the second and more relevant point, a similarly greater prevalence of concurrent thyroid nodular disease in patients with primary than in patients with secondary HPT had also been reported by De Feo *et al.* (12) in a smaller population sample (44% compared with 29%, in a group of 49 patients with HPT in whom the cumulative prevalence of coexisting thyroid nodular disease was 38.9%); however, the authors did not further analyze this finding, which was not the primary object of their investigation.

These observations may suggest that the increased endogenous calcium concentrations or turnover (a peculiar feature of primary but not of secondary HPT) act as a growth factor promoting the development of goiter in patients. Although direct experimental evidence is lacking in humans, this hypothesis is consistent with some early experimental data obtained in animals (14), and with some of the earliest epidemiological observations in humans (46). In contrast, speculation about the possible role of PTH acting by itself as a goitrogenic factor in hyperparathyroid patients is undermined by the observation that the prevalence of concurrent thyroid nodular disease was significantly lower in patients with secondary HPT, in whom the average serum PTH concentrations were about fivefold greater than those in patients with primary HPT.

Of course, the possible role of calcium as a goitrogenic factor does not exclude the possibility that other growth factors found in excess concentrations in patients with HPT (47), irrespective of primary or secondary HPT, also may be goitrogenic. In this regard, HPT is known to induce increased concentrations of epithelial growth factor and insulin-like growth factor-I (47). In experimental models, these growth factors proved to be goitrogenic on isolated swine thyroid follicles (48), their effect being modulated by thyrotropin (49).

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