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High Prevalence of Thyroid Ultrasonographic Abnormalities in Primary Aldosteronism

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The study was performed to evaluate the prevalence of thyroid abnormalities detected by ultrasonography and, in particular, of multinodular nontoxic goiter in primary aldosteronism. We analyzed 80 consecutive of patients with primary hyperaldosteronism (40 with unilateral adenoma and 40 with idiopathic hyperaldosteronism) and 80 normotensive healthy controls, comparable for age, sex, iodine intake, and geographical area. Blood pressure, thyroid palpation, thyroid function, and ultrasonography were evaluated. The prevalence of ultrasonographic thyroid abnormalities was 60% in primary aldosteronism and 27% in controls ($p < 0.0001$). There was a statistically significant difference in prevalence of these abnormalities in unilateral adenoma and idiopathic hyperaldosteronism with respect to controls ($p < 0.05$ and $p < 0.0001$, respectively). The prevalence of multinodular nontoxic goiter in idiopathic hyperaldosteronism was higher than in controls ($p < 0.001$) and, in particular, in female patients. From these data it seems to be worth considering the existence of primary hyperaldosteronism in patients with multinodular goiter and hypertension.

Key Words: Primary hyperaldosteronism; thyroid abnormalities; ultrasonography; multinodular goiter.

Introduction

Primary hyperaldosteronism is characterized by an increase in aldosterone, suppression of plasma renin activity (PRA), increased aldosterone/PRA ratio in the upright position, and lack of response of aldosterone to volume expansion *(1,2)*. The most common forms of the disease are solitary aldosterone-producing adenomas and idiopathic hyperaldosteronism. A glucocorticoid remediable hyperaldosteronism has also been described *(1,3)*. Primary hyperaldosteronism is rarely associated with acromegaly *(1,4)*, pheochromocytoma *(3)* Cushing's syndrome, and hyperprolactinemia *(1)*. In some rare cases primary hyperaldosteronism is one of the manifestations of type I multiple endocrine neoplasia (MEN I) *(1,5)*. The genesis of idiopathic hyperaldosteronism can involve an increased sensitivity to angiotensin II or other factors that hyperstimulate the physiological synthetic processes in the adrenals *(1)*.

The prevalence of thyroid nodules, evidenced by palpation, in the general population was estimated to be between 4% and 7% *(3,6,7)*. In the past decades, the use of high-frequency ultrasonography has shown a higher prevalence of nonpalpable nodules. In a study done in a North American population, 67% of the subjects had thyroid nodules, evidenced by ultrasonography *(8)*. Using this device, two studies, one performed in Europe and one in South America, have found a lower prevalence of thyroid nodules in the general population: 17% in the study of Tomimori et al. in Brazil *(9)*, 27% by Brander et al. in Finland *(10)*, 30% by Knudsen et al. in Denmark *(11)*, and 19% by Woestyn et al. in Belgium *(12)*. In a recent study performed in Italy, the prevalence of thyroid nodules was 18% *(13)*. Several factors may explain the variability of prevalence such as iodine intake and age of the subjects. Thyroid nodules are more frequent with age, being the highest between 56 and 65 years.

The rationale of our study was the clinical observation of palpatory multinodular goiter in patients with primary hyperaldosteronism. We carried out a study on the prevalence of thyroid abnormalities in a series of patients with primary aldosteronism and in healthy controls.

Results

Thyroid function was normal and not statistically different in the patients and controls (Fig. 1). The prevalence of thyroid abnormalities at ultrasonography among patients with primary hyperaldosteronism was 60% (75% in the idiopathic form and 45% in unilateral adenoma). The prevalence was significant in primary aldosteronism versus controls ($p < 0.0001$), and in both forms of aldosteronism versus controls (Table 1). In particular, the occurrence of multinodular nontoxic goiter was 23.8% in the patients and 6.3% in

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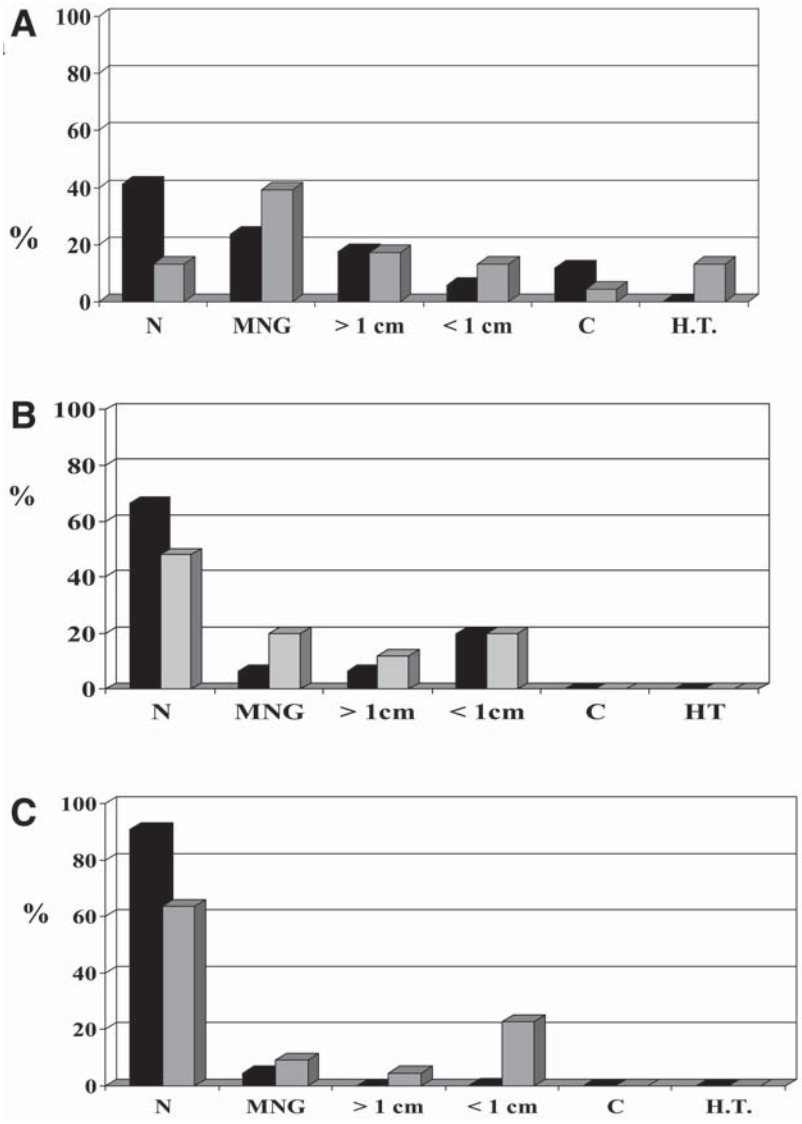

Fig. 1. Percentage (%) of thyroid abnormalities in (**A**) male and female patients ($n = 40$) with primary aldosteronism due to idiopathic hyperaldosteronism, (**B**) in male and female patients ($n = 40$) with primary aldosteronism due to unilateral adenoma, and (**C**) in male and female controls ($n = 52$). N = normal; MNG = multinodular goiter; >1 cm = nodules >1 cm; <1 cm = nodules <1 cm; C = carcinoma; HT = Hashimoto's thyroiditis. (Black columns = female; grey columns = male.)

controls ($p < 0.01$). Three subjects with idiopathic hyperaldosteronism had papillary carcinoma, and three had autoimmune thyroiditis. Eighteen percent of controls had small nodules (< 1 cm of diameter) and 2.5% showed solitary nodules > 1 cm in diameter. In 25% of the patients and in 70% of the controls who had thyroid abnormalities at ultrasound analysis, palpation was negative. In only 4 of the 24 cases of multinodular goiter, the palpation was negative, and the finding was not known before performing ultrasonography.

We have also considered the relative prevalence of thyroid abnormalities with respect to the sex of the subjects (Fig. 1). The thyroid was normal at ultrasonography in 66% of males and in 48% of females with aldosterone-producing adenoma, in 41% males and 13% female with idiopathic form, and in 85% of male and 57.4% of female controls. The prevalence of multinodular goiter was higher in female than in male patients (adenoma: female 20%, male 7%; hyperplasia: female 39%, male 23%; controls: female 6.5%, male 5.8%). The power of the analysis for an α value of 0.05 was 0.848, when patients were compared to controls, and 0.797 when the patients with adenoma were compared to those with idiopathic hyperaldosteronism.

We did not find any correlation between the duration of the adrenal disease and the prevalence of thyroid abnormalities or between the age of the subjects and thyroid abnormalities either in patients or in controls. The prevalence of

Table 1
Prevalence of Thyroid Abnormalities in Primary Hyperaldosteronism and In Controls

	Primary Aldosteronism			
	Adenoma	Idiopathic Aldosteronism	All Cases	Controls
Gender: *n* (%)				
M	15 (37.5%)	17 (42.5%)	32 (40%)	34 (44%)
F	25 (62.5%)	23 (57.5%)	48 (60.5%)	46 (56%)
Age	51.0 (19–71)	55.5 (27–76)	53.0 (19–76)	50.5 (20–74)
Thyroid picture: n (%)				
Nodule <1 cm	8 (20%)	4 (10%)	12 (15%)	15 (18.7%)
Nodule >1 cm	4 (10%)	7 (17.5%)	11 (13.7%)**	2 (2.5%)
Papillary carcinoma	0	3 (7.5%)	3 (3.7%)	0
Multinodular goiter	6 (15%)	13 (32.5%)	19 (23.8%)**	5 (6.3%)
Autoimmune thyroiditis	0	3 (7.5%)	3 (3.7%)	0
All abnormalities	18 (45%)	30 (75%)	48 (60%)**	22 (27.5%)
Normal	22 (55%)	10 (25%)	32 (40%)	58 (72.5%)
Thyroiod function (mean ± SD)[§]				
Free-T3 (pmol/L)	4.6 ± 0.5	4.8 ± 0.9	4.7 ± 0.7	4.9 ± 0.6
Free-T4 (pmol/L)	13.5 ± 3.5	13.4 ± 3.0	13.4 ± 3.1	13.3 ± 2.9
TSH (mU/L)	2.0 ± 1.1	1.9 ± 1.0	2.0 ± 1.0	1.9 ± 0.6

**$p < 0.01$ (all cases versus controls).
[§]The cases of Hashimoto's thyroiditis were not included.

thyroid abnormalities was not significantly different in subjects with primary aldosteronism who had or had not undergone surgery.

Discussion

The prevalence of thyroid abnormalities at ultrasonography is relatively high in healthy controls, and our data are consistent with those reported in two other studies done in Europe *(10,11)*. In other studies *(9,12,13)*, the prevalence of thyroid nodules was different and the discrepancy can be related to different iodine intake, age of the population, and size of thyroid lesions considered to be a nodule. In any case, the occurrence of multinodular nontoxic goiter in primary aldosteronism is frequent, while it is rare in the general population.

We also found other thyroid abnormalities like papillary carcinoma, autoimmune thyroiditis, and solitary nodules, but in this case we cannot claim with certainty a linkage with primary hyperaldosteronism owing to the relatively small number of subjects affected. It is, however, worthy of note that the three cases with papillary carcinoma all had idiopathic hyperaldosteronism. Primary hyperaldosteronism due to unilateral adenoma has been described in type I multiple endocrine neoplasia (MEN I) syndrome in association with prolactinoma, hyperparathyroidism, and toxic multinodular goiter *(1,5)* Multinodular nontoxic goiter has not been reported in this syndrome. In a recent study *(14)*, done in a large series of acromegalic patients, an increased prevalence of thyroid disorders, particularly nontoxic nodular goiter has been described.

Some mechanisms can be hypothesized to explain the association between idiopathic hyperaldosteronism and multinodular nontoxic goiter. Adrenocorticotropin and angiotensin II are the classical regulators of adrenocortical growth, but other regulators can also play an important role at the thyroid and adrenal level. We can also speculate that there may be a generalized increased incidence of nodularity in various tissues. An imbalance between growth factors (cytokines) and growth inhibitors could have a role in the pathogenesis of these combined diseases, i.e., idiopathic hyperaldosteronism and multinodular nontoxic goiter *(1,2,15–17)*. A recent study has also demonstrated an increased aldosterone concentration in benign colloid nodules and the presence of aldosterone synthase expression at the level of thyroid tissue *(18)*. These results are consistent with a possible common pathogenetic mechanism in the concomitant occurrence of thyroid and adrenal nodules. A defect of deiodinase, causing inhibition of dopamine synthesis and subsequent hyperaldosteronism, could also be involved in our findings *(19)*. It is, in effect, known that dopamine antagonists, like metoclopramide, stimulate aldosterone secretion *(20)*.

An important question to be addressed is whether or not primary hyperaldosteronism antedates the thyroid abnormalities. In one case of idiopathic hyperaldosteronism, ultrasonography of the thyroid was normal at the moment of diagnosis. Three years later, multinodular goiter was evident at both clinical and ultrasound observation. In addition, in most of the patients with primary hyperaldosteronism and thyroid abnormalities who were reevaluated at a distance from the diagnosis, thyroid palpation was reported negative in the patient's record of previous hospitalizations. We therefore suppose that the clinical picture of primary aldosteronism antedates the thyroid abnormalities.

From all these considerations it can be hypothesized that the high prevalence of multinodular goiter in primary hyperaldosteronism could be considered an endocrine association. We therefore suggest a thyroid ultrasonography in all cases of primary hyperaldosteronism and to consider the possibility of primary hyperaldosteronism in subjects with multinodular goiter and hypertension. This is very important, because it has recently been reported that the prevalence of primary hyperaldosteronism is higher than previously thought among patients with hypertension (about 10% of patients with hypertension) and in most cases serum potassium is normal *(1,21)*.

Patients and Methods

From January 1998 to January 2001 we studied 80 patients who presented consecutively to our Department with proven primary hyperaldosteronism (32 male and 48 female). Symptoms of familiarity for thyroid functional or echographic abormalities were present in 21% of the patients (32% of the patients with idiopathic form and 10% of patients with adenomas). None of the patients had symptoms of hyperaldosteronism. Serum potassium was reduced in 56% of the patients. Aldosterone-receptor antagonists were withdrawn 1 mo before and other hypotensives 15 d before performing hormonal evaluation.

The diagnosis was made by measuring PRA, aldosterone, aldosterone/PRA ratio in the upright position, and aldosterone after a saline suppression test. The diagnosis of form and site was done with the postural test, adrenal computerized tomography or magnetic resonance imaging, and adrenal scintigraphy with ^{75}Se-cholesterol after suppression of ACTH with dexamethasone. Adrenal vein sampling, for measurement of plasma cortisol and aldosterone, was performed when the diagnosis was still unclear.

We identified 40 patients with unilateral aldosterone-producing adenoma (25 female and 15 male, median age 51, range 19–71 yr) and 40 with idiopathic hyperaldosteronism (23 female and 17 male, median age 55.5 yr, range 27–76 yr, Mann–Whitney test $p > 0.05$ versus controls in both groups). In 12 cases with adenoma, ultrasound analysis was performed before surgery, whereas the other cases had undergone surgery prior to examination.

The results were compared with those of a group of 80 consecutive healthy, informed, normotensive controls (34 male and 46 female, median age 50.5 yr, range 20–74 yr), comparable for age distribution, sex, geographical area, and iodine intake (about 100 μg/d). The controls were recruited from outpatients coming to our Institute. The criteria of selection of controls was the absence of hypertension and of known thyroid diseases. A familial incidence for thyroid diseases was reported in the history of 6% of the subjects. In both patients and controls, thyroid palpation, thyroid function, antithyroid antibodies, and thyroid ultrasonography were evaluated after full explanation of the purpose and nature of these procedures. When necessary, a fine-needle aspiration was also performed.

Multinodular nontoxic goiter was defined as enlarged irregular thyroid containing nodules within its substance, in subjects with normal thyroid function and TSH. Unilateral nodule was defined as a hypo-, iso-, or hyper-echogenic nodule with complete or incomplete surrounding transonic ring, in absence of other ultrasonographic abnormalities. Nodules were further subdivided in relation to their diameter as < 1 cm or > 1 cm. The diagnosis of thyroiditis was made upon echographic picture, showing hypoechogenic irregular pattern, and areas of hypervascolarization at the color Doppler. This finding was associated with positivity of antithyroid antibodies.

The thyroid ultrasonography was performed in all cases by the same operator using the same machine (ESAOTE AU3, probe 7.5 or 10 MHz). The study was completed in 4 mo and the ultrasonographer was blinded as to the diagnosis (normal controls versus primary aldosteronism).

Thyroid hormones, TSH, and antithyroid antibodies were measured by chemiluminescence (BLKGULDEN) using a standardized autoanalyzer.

Data were stored in a PC and evaluated by "Statistica" package software (Statsoft, Inc.). The difference in age and sex distribution was evaluated by the Mann–Whitney test.

The difference in categorical items was evaluated by χ^2 and Fisher exact test, and the grade of significance was expressed by $p < 0.05$.

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