

## CLINICAL STUDY

# Primary thyroid disorders in endogenous Cushing's syndrome

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## Abstract

**Objective:** To study the prevalence of primary thyroid disorders in patients who underwent endogenous hypercortisolism.

**Design:** Retrospective evaluation of 59 patients with Cushing's syndrome (CS) who had, at least, a record of thyroid palpation by expert endocrinologists and basal measurements of TSH by second generation assays. When available, tri-iodothyronine and thyroxine serum levels, TRH-TSH tests and anti-thyroid antibodies were also analyzed. There were two age- and gender-matched control groups. The 'goiter control group' comprised 118 healthy subjects who underwent thyroid palpation. The 'antibody control group' was composed of 40 individuals who attended the blood bank of our hospital. Antibodies against thyroperoxidase and measurements of TSH were analyzed in their blood samples.

**Methods:** Available files of 83 CS patients admitted to our endocrine unit from 1985 to 1998 were examined. Fifty-nine patients (52 women and 7 men) with a mean age of 36.2 years (range 14–61 years) met the above requirements. Diagnosis of hypercortisolism had been established by a standard 1-mg overnight dexamethasone suppression test and urinary free cortisol (UFC). Etiological diagnosis involved dynamic testing, measurements of ACTH levels and imaging techniques. After treatment, all but one of the patients were cured or controlled of their hypercortisolism. This was established by the finding of subnormal serum cortisol concentrations and/or subnormal 24-h UFC levels. Primary thyroid disorders were defined by the presence of one or more of the following diagnostic criteria: (i) goiter, (ii) positive anti-thyroid antibodies and/or (iii) primary thyroid function abnormalities.

**Results:** Eighteen (30.5%) patients had goiter (diffuse in 78% and nodular in 22%), 14 (23.7%) had primary subclinical hypothyroidism and 5 (8.4%) had hyperthyroidism. In 41 patients evaluated for antithyroid antibodies, it was found that 23 (56.1%) had positive titers. In a group of patients in which thyroid autoantibodies were measured both before and after resolution of hypercortisolism, prevalences of positive titers were 26.7% and 86.7% respectively ( $P = 0.001$ ). The overall frequency of primary thyroid abnormalities in our patients with Cushing's syndrome was 55.9%.

**Conclusions:** Patients with endogenous Cushing's syndrome exhibit a remarkably high prevalence of primary thyroid disease. Resolution of hypercortisolism seems to trigger the development of autoimmune thyroid disorders in presumably predisposed subjects.

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## Introduction

Endogenous Cushing's syndrome (CS), as well as exogenous administration of glucocorticoids, may alter the performance of the hypothalamic–hypophyseal–thyroid axis in several ways (1). Thyrotropin releasing hormone (TRH) release is disturbed in adult patients with Cushing's disease (CD) (2) and after administration of glucocorticoids in healthy volunteers (3). Both thyrotropin (TSH) pulses and the nocturnal serum TSH surge are abolished in patients with adrenocorticotropin (ACTH)-dependent CS (2) and after hydrocortisone infusion (3, 4).

Recently, there have been a few case reports showing that resolution of hypercortisolism may be

followed by the emergence or worsening of autoimmune thyroid disease (5–9). It has also been suggested that CD patients display a higher prevalence of nodular thyroid disease as compared with the general population (10). In view of available findings for these associations and given the large number of CS patients attending our hospital, we evaluated such cases in order to define the frequency of primary thyroid disorders and to attempt to establish whether there is a relationship between remission of hypercortisolism and development of primary thyroid disorders. Interestingly, concurrently with the development of our present work, Colao *et al.* (11) carried out a closely related study in Italy disclosing similar findings.

## Patients and methods

Available files of 83 CS patients admitted to our endocrine unit from 1985 to 1998 were retrospectively examined. All CS cases with a record of palpation of the thyroid gland, performed by expert endocrinologists, and at least one measurement of basal serum TSH by second generation assays, were selected for inclusion. Fifty-nine patients, (52 women and 7 men), with a mean age of 36.2 years (range 14–61 years) met these minimum requirements. When available, pre- and/or post-surgical data of a TRH-TSH test, serum peripheral levels of tri-iodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ) and anti thyroid microsomal antibodies (MCHA) performed by hemagglutination assays and/or anti-thyroperoxidase antibodies (TPO-Ab), as well as antithyroglobulin antibodies (TG-Ab), measured by standard ultrasensitive techniques, were also evaluated. Diagnosis of hypercortisolism had been established by an overnight low dose dexamethasone suppression test (Nugent's test) (12) and urinary free cortisol (UFC) measured in 24-h and spot (22 to 23 h) samples (13, 14). Etiological diagnosis was made by: (i) dynamic testing (8 mg dexamethasone suppression test) (15, 16) and, in two patients with doubtful results, a corticotropin releasing hormone (CRH)-desmopressin test (17); (ii) measurement of ACTH levels; and (iii) imaging techniques (sellar region magnetic resonance imaging (MRI) and/or lung and adrenal computed tomography scan). Fifty-two out of the fifty-nine patients had their etiological diagnosis confirmed by histology (including immunostaining of pituitary adenomas) and/or by partial or complete restoration of the eucortisol state after pituitary surgery, pituitary radiotherapy, unilateral adrenalectomy or resection of lung carcinoid. In five additional patients, even though they were not operated (three because of associated empty sella and two with normal pituitary MRI), unequivocal results of dynamic tests were considered sufficient diagnostic evidence for CD. As a result of the application of such criteria, 48 patients had CD, eight had Cushing's syndrome due to an adrenal adenoma and one had ectopic ACTH syndrome due to a lung carcinoid. The source of hypercortisolism was unidentified in two patients.

Pituitary surgery (selective adenectomy or partial hypophysectomy) was performed in 43 out of the 48 patients with CD. Radiotherapy, using either linear accelerator or gamma-knife stereotactic radiosurgery, was performed in five patients. It was employed as primary treatment in two patients (gamma-knife) and as a complementary procedure after failure of surgery in three patients (external radiotherapy). Three additional patients, who failed to achieve remission with pituitary surgery and radiotherapy, underwent bilateral adrenalectomy. Remission of CD after surgery was established on the basis of the following criteria:

subnormal serum cortisol concentrations and/or subnormal 24-h UFC levels.

Thirty-two patients with CD achieved remission of hypercortisolism by pituitary surgery and/or radiotherapy. Eleven patients with persistent CD after pituitary surgery and/or radiotherapy were treated with ketoconazole. With the exception of one patient with a macroadenoma (who failed to improve, despite several therapeutic procedures), all CD patients had resolution of hypercortisolism. All eight patients with CS due to an adrenal adenoma were successfully treated by unilateral adrenalectomy and the one with an ectopic ACTH syndrome was cured after resection of a bronchial carcinoid. Two patients, in whom the source of hypercortisolism was unidentified, remained eucortisol under medical treatment with ketoconazole.

A patient was defined as having primary thyroid disorders by one or more of the following diagnostic criteria: (i) goiter, (ii) positive anti-thyroid antibodies, and/or (iii) primary thyroid function abnormalities. Primary hypothyroidism was classified in four stages: stage I, with high normal basal serum TSH levels (2–5 mIU/l) and hyper response of TSH to TRH (18); stage II, raised TSH levels (> 5 mIU/l) with normal  $T_3$  and  $T_4$  levels; stage III, raised TSH levels, low  $T_4$  and normal  $T_3$  levels; and stage IV, raised TSH levels, low  $T_3$  and  $T_4$  levels. Stages I and II were regarded as subclinical hypothyroidism. It should be pointed out that all CS patients were living in iodine sufficient areas of Argentina.

## Control groups

Two control groups were used for this study and procedures were applied in agreement with the ethical guidelines of our hospital committee on human experimentation. The 'goiter control group', comprising 118 healthy subjects matched by age and gender with CS patients, was only used for detecting goiter through thyroid palpation. The second control group ('antibody control group') consisted of a further 40 healthy individuals who attended the blood bank of our hospital. An aliquot of their donated blood was employed for measuring TPO-Ab and TSH.

All control subjects denied having known thyroid diseases or relatives with any kind of thyroid disorders. The composition of all groups, according to age and gender, is shown in Table 1.

## Statistical analysis

Data were expressed as means  $\pm$  S.E.M. Statistical analysis was performed by SPSS for Windows version 8.0 (Cary, NC, USA). Comparisons between the numerical data were performed by Student's *t*-test for

**Table 1** Composition of all groups of patients according to age and gender.

Group	n	Female		Male		Age (years)	
		n	%	n	%	Mean	Range
Cushing's syndrome	59	52	88.1	7	11.9	36.2	14-63
Goiter control	118	104	88.1	14	11.9	36.8	14-63
Antibody control	40	35	87.5	5	12.5	35.3	20-59

unpaired data and comparisons between categorical data by Chi square test with Yates' correction. The P values are given for these analyses. Significance was set at 5%.

**Results**

The overall rate of primary thyroid disorders (PTD), diagnosed either before or after resolution of hypercortisolism, was 55.9% (33/59) in the CS population. Figure 1 provides an overview of all thyroid disorders and the patient distribution within each category as regards thyroid autoimmunity, thyroid function and goiter.

**Thyroid palpation**

Eighteen (30.5%) patients had goiter, which was diffuse in 13 (78%) and nodular in 5 (22%) patients. Fine needle aspiration cytology of the nodules showed that one of them was a papillary carcinoma. In the goiter control group 8.5% had goiter, and only 2.5% nodular goiter, disclosing a statistically significant difference versus the CS group (P = 0.008). However,

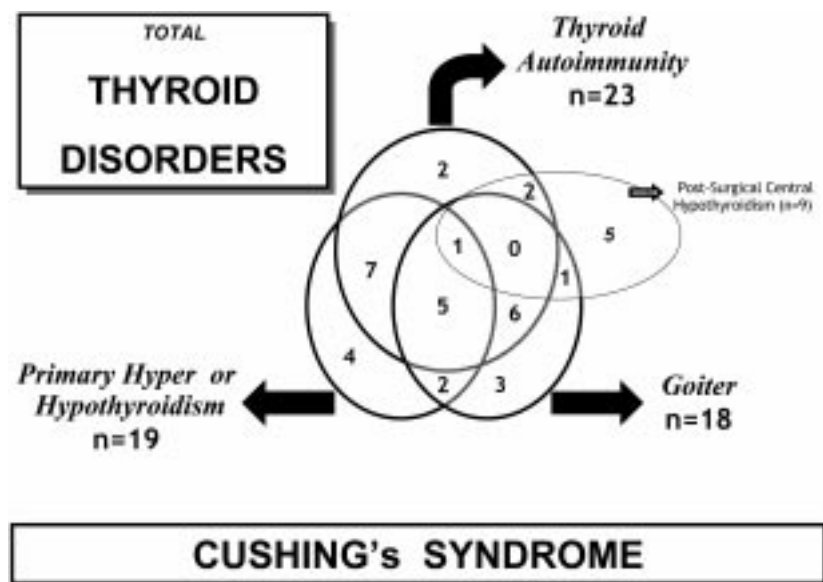
the diffuse/nodular goiter ratio was similar for both groups (CS = 2.6 vs goiter control group = 2.3).

**Primary thyroid function abnormalities**

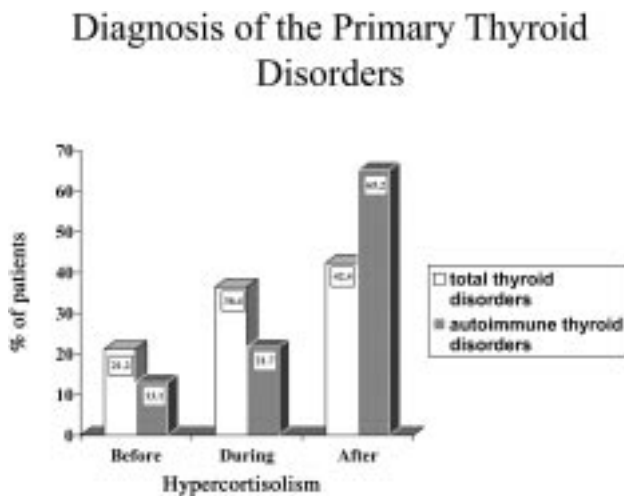
These were found in 19/59 of CS patients (32.2%) and in 19/33 (58%) of those with PTD. Fourteen patients (23.7%) had primary subclinical hypothyroidism (five in stage I and nine in stage II). Only 2.5% of the antibody control group had subclinical hypothyroidism (P < 0.001). Five CS patients had hyperthyroid Graves' disease (8.4% of all CS patients and 15.2% of those with PTD). One patient had Graves' disease diagnosed 20 years before the onset of CD. In the remaining four patients (two with CD and two with adrenal adenoma), hyperthyroidism was diagnosed 3, 14, 18 and 100 months respectively after resolution of hypercortisolism.

**Thyroid autoimmunity**

Considering the entire group, it was found that among 41 patients evaluated for the presence of anti thyroid antibodies, pre and/or post surgery, 23 (56.1%) had evidence of thyroid autoimmunity. In patients with PTD in whom the antibodies were measured, the prevalence of positive titers was 79.3% (23/29). 10% of the antibody control group had positive TPO-Ab (P < 0.001). In a previous study performed by one of us (H N) in 1984, 8% of control women had positive titers of MCHA (19).



**Figure 1** Overview of total thyroid disorders in 38 patients with CS, showing the distribution of cases within each category regarding thyroid autoimmunity, thyroid function, goiter, and post-surgical central hypothyroidism.



**Figure 2** Diagnostic time of total primary thyroid disorders ( $n = 33$ ) and autoimmune thyroid disorders ( $n = 23$ ) in relationship to the hypercortisolism status of the CS patients.

### Detection of primary thyroid disorders and their relationship with CS diagnosis

As shown in Fig. 2, PTD was recognized before the diagnosis of CS in 21.2% of cases, at the time of the diagnosis of CS in 36.4% of cases, and after resolution of hypercortisolism in 42.4% of cases. When only patients with thyroid autoimmunity were considered ( $n = 23$ ), detection of thyroid disease was achieved before diagnosis of CS in 13.1% of cases, at the time of diagnosis in 21.7% of cases and after remission of hypercortisolism in 65.2% of cases.

### Central hypothyroidism

Nine patients had central hypothyroidism (low  $T_4$  and TSH levels) after trans-sphenoidal surgery and radiotherapy, four of whom also had PTD (see Fig. 1).

### Thyroid hormone profile in CS patients pre- and post-hypercortisolism treatment

$T_3$ ,  $T_4$  and TSH values of the different subgroups of CS patients, as well as the TSH levels of the antibody

control group, are shown in Table 2. As can be seen, TSH concentrations are higher in PTD patients. These increases were even greater after resolution of hypercortisolism. There were no statistical differences between  $T_3$  and  $T_4$  levels in euthyroid or PTD patients, either pre- or post-resolution of hypercortisolism.

### Follow-up studies in PTD patients

Some patients were studied pre- and post-resolution of hypercortisolism, and PTD appearance or progression was evaluated more thoroughly. In a group of eight patients without thyroid abnormalities at the time of CS, six showed a transition to PTD after CS remission; five of them developed thyroid autoimmunity as follows: one Graves' disease (8 years after), two Hashimoto's thyroiditis with subclinical hypothyroidism (12 and 13 months after surgery), and a further two showed only positive titers of thyroid antibodies (2 and 3 months post surgery). The sixth patient, who had no evaluation for anti-thyroid antibodies, developed subclinical hypothyroidism 2 months after becoming eucortisolic. In seven additional patients, PTD had been diagnosed before CS treatment, but there was progression or worsening of these disorders, in most cases, after becoming eucortisolic (see Fig. 3).

In the 15 patients of this group, evaluated for thyroid autoimmunity, prevalence of positive anti thyroid antibodies titers was 26.7% (4/15) during active CS, and 86.7% (13/15) after resolution of hypercortisolism ( $P = 0.001$ ) (Fig. 4). Unfortunately, due to the retrospective nature of the study, we were unable to compare the different titers of thyroid antibodies. Thus, we only divided them into positive and negative.

### Mean diagnostic time of PTD in eucortisolic patients

PTDs were diagnosed at a mean time of 9.8 months (range 2–18 months) after normalization of adrenal function. Two cases were excluded from this analysis: one with a diagnosis of subclinical hypothyroidism and positive thyroid autoimmunity found 27 years after CD remission, and another

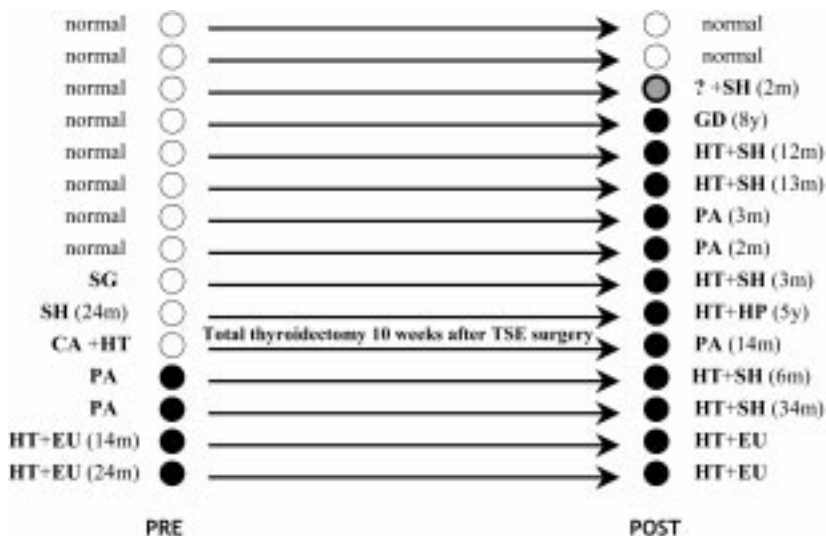
**Table 2** Thyroid hormone profile.

Group	$T_3$ (ng/dl)	$T_4$ ( $\mu$ g/dl)	TSH (mIU/l)	P (for TSH values)
CS euthyroid patients (active)	113 $\pm$ 13	7.1 $\pm$ 0.5	1.7 $\pm$ 0.2	NS vs CS euthyroid (post-treatment)
CS euthyroid patients (post-treatment)	128 $\pm$ 11	7.3 $\pm$ 0.7	1.9 $\pm$ 0.4	<0.001 vs CS PTD (post-treatment)
CS PTD patients* (active)	117 $\pm$ 8	7.1 $\pm$ 0.4	3.7 $\pm$ 0.8	<0.001 vs CS euthyroid (active) and <0.01 vs CS euthyroid (post-treatment)
CS PTD patients* (post-treatment)	122 $\pm$ 14	7.8 $\pm$ 0.4	6.6 $\pm$ 2.0	<0.01 vs CS PTD (active)
Antibody control group	—	—	1.54 $\pm$ 0.13	NS vs CS euthyroid

\*Hyperthyroidism excluded.

NS = not significant.

Normal values:  $T_3 = 70$ –190 ng/dl;  $T_4 = 4.5$ –12  $\mu$ g/dl; TSH = 0.5–5.0 mIU/l.



**Figure 3** Follow-up of 15 patients whose thyroids were evaluated prior to and/or at the time of CS diagnosis. Eight patients were normal and the other seven were abnormal. Six of the eight normal thyroids developed primary disorders after resolution of CS, while five initially affected patients showed progression or worsening of the PTD after controlling the hypercortisolism. Two other euthyroid patients with Hashimoto's thyroiditis remained in the same condition after cortisol normalization. Each pair of horizontal circles represents a single patient, before and after CS remission. Open circles, negative antibodies; solid circles, positive antibodies; grey circle with dark outline, no evaluation of thyroid autoantibodies. SH, subclinical hypothyroidism; HP, clinical hypothyroidism; GD, Graves' disease; HT, Hashimoto's thyroiditis; PA, only positive anti thyroid antibodies; SG, simple goiter; CA, papillary carcinoma; EU, functional euthyroidism (normal T<sub>3</sub>, T<sub>4</sub> and TSH); TSE, trans-septum-sphenoidal. Values in brackets represent the time of diagnosis of thyroid disorder (m, months; y, years).

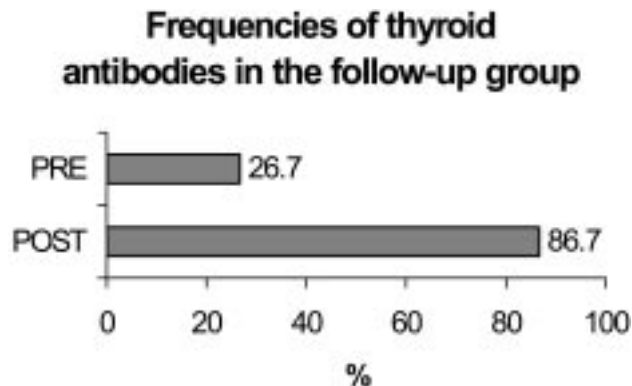
who developed Graves' disease 8 years after resolution of hypercortisolism (see above).

**Discussion**

In this series of patients with endogenous Cushing's syndrome we found a high frequency of thyroid autoimmunity (56.1%), compared with the prevalence in the control group (10%). Moreover, we also found a high rate of subclinical hypothyroidism (23.7%) compared with that published in the world literature for the general population, which ranges from 2.5 to 10.4% (20–22), and compared with our control group (2.5%).

We also found a higher frequency of goiter (30.5%) in Cushing's patients as compared with the control group (8.5%). In our CS population, the prevalence of nodular thyroid disease by palpation was 8.4% (n = 5), whereas in control subjects it was barely 2.5%. This finding is similar to that of a survey of Semple & Thompson (23), who reported an increased prevalence of thyroid nodules in 50 patients with CS compared with that commonly found in the UK population (10% vs 4%). When patients were evaluated by ultrasonography, Invitti *et al.* (10) found a significantly higher prevalence of nodular thyroid disease (60%) in patients with CD, with respect to a group of control subjects in whom the prevalence of thyroid nodules was comparable to that reported for the general population in Europe (20%). It has been proposed that CD cases may present an increased proliferation of thyrocytes through raised interleukin-6 levels secreted by tumoral corticotropic cells (24, 25).

Interactions between Cushing's syndrome and autoimmune diseases have not yet been studied deeply. However, there are several case reports of exacerbation of autoimmune hypothyroidism or Graves' disease following partial hypophysectomy or adrenalectomy (5–9). There is also evidence of the onset of rheumatoid arthritis (26, 27) and systemic lupus erythematosus (28) after surgical treatment of CD. The main pituitary-dependent hormone that influences immune reactions is cortisol, which inhibits most aspects of the immune response, including proliferation of lymphocytes. Glucocorticoids are known to suppress autoimmune reactions through the reduction in T cell proliferation (29), and have been used to treat patients with Hashimoto's thyroiditis. In such patients, glucocorticoids may decrease anti thyroid antibody



**Figure 4** Frequency of thyroid antibodies in the 15 patients of the follow-up group, pre- and post-resolution of the hypercortisolism. The patient without evaluation of thyroid autoantibodies (see Fig. 3) was considered as having positive antibodies for the practical purpose of this calculation.

titers and normalize thyroid function (30). Likewise, it has been suggested that patients with thyroid autoimmunity may be 'protected' from autoimmune thyroid dysfunction by the development of Cushing's syndrome, because of the immunosuppressor activity of hypercortisolism (5). After restoration of normal pituitary–adrenal function (removal of adrenal or pituitary adenomas), the autoimmune process may be exacerbated and overt thyroid dysfunction is liable to develop. The development of autoimmune thyroid disorders after the cure of patients with CS could mimic what happens in postpartum thyroiditis. Pregnancy is a time of immune suppression, followed by a postpartum immunological rebound (31). Moreover, cortisol production has been shown to be augmented in normal pregnancy (32).

Our study included a series of patients with endogenous Cushing's syndrome displaying an increased prevalence of autoimmune thyroid disease both before and especially after hypercortisolism was adequately treated. Follow-up showed that the prevalence of positive anti thyroid antibodies during active disease (26.7%) increased sharply (86.7%) after hypercortisolism was resolved. These findings closely agree with those of Colao *et al.* (11), who documented an increased prevalence of TG-Ab and TPO-Ab positive titers in patients after CD remission as compared with those observed in the same subjects during active disease (20% and 40% pre- and post-successful pituitary surgery). It is also remarkable that four out of our five cases of Graves' disease developed hyperthyroidism after CS remission, but in the fifth patient this developed 20 years before the onset of CS, which could argue against a relationship between the two conditions in this patient. Mean diagnostic time for primary thyroid disorders arising after resolution of hypercortisolism was 9.8 months (range 2–18 months) in most cases. This brief period seems clearly related to the onset or progression of thyroid autoimmunity concomitantly with hypercortisolism remission.

Since the association of PTD and CS goes even further than the merely immunosuppressive effect already discussed, it seems that the nature of this relationship, that remains obscure, should be more complex and perhaps related to the genetic background of the patients.

Serum tri-iodothyronine levels may be decreased under glucocorticoid administration, as a result of a reduction in serum thyroxine binding protein and by inhibition of T<sub>4</sub> monodeiodination in peripheral tissues. However, we failed to find low T<sub>3</sub> levels during active disease. Overall, our results agree with those from Colao *et al.* (11). It is probable that endogenous levels of hypercortisolism may not be enough to produce this effect. Interestingly, no statistically significant differences were found between TSH levels during active disease and after CS resolution in euthyroid

patients, although they were clearly observed in the PTD group, as previously described (11).

Based on our findings, we suggest that thyroid function and antithyroid antibodies, as well as thyroid morphology, should be evaluated carefully before and after CS remission. Since the risk of autoimmune thyroid dysfunction in CS cases is considerable, we recommend long-term follow-up, since thyroid autoimmune disorders may appear many years after resolution of endogenous hypercortisolism.

In conclusion, beyond the limitations of the retrospective nature of this study, we have demonstrated a remarkably high prevalence of primary thyroid disorders in patients with endogenous CS, which strongly supports our contention that resolution of hypercortisolism triggers the development of autoimmune thyroid disorders in predisposed subjects.

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