The Nocturnal Serum Thyrotropin Surge Is Inhibited in Patients with Adrenal Incidentaloma

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ABSTRACT

Background: **Alterations in hypothalamic-pituitary function have been described in patients with incidentally discovered adrenal adenomas and have been attributed to their subtle hypercortisolemic status.**

Methods: **To establish whether the central control of the hypothalamic-pituitary-thyroid axis is altered in these endocrine conditions, the nocturnal (10:30 PM–2:00 AM) serum thyroid-stimulating hormone (TSH) surge (measured by dividing the difference between nighttime and morning TSH values by the morning TSH value and then multiplying by 100), the TSH response to thyrotropin-releasing hormone (200 μg as an intravenous bolus) and serum free thyroid hormone levels were evaluated in patients with adrenal incidentaloma (experimental group) and in normal controls (control group). Urinary free cortisol concentrations were also measured.**

Results: **The nocturnal TSH surge was observed in the normal controls, whereas it was inhibited in the patients of the experimental group. Serum free triiodothyronine levels were similar in the two groups, whereas the TSH response to thyrotropin-releasing hormone was significantly lower in the experimental than in the control group. Urinary free cortisol levels were significantly higher in the experimental group.**

Conclusion: **These data indicate that even conditions of slight glucocorticoid excess may exert inhibitory effects on TSH secretion, which suggests the presence of a slight central hypothyroidism in patients with adrenal incidentaloma. (J Investig Med 2002;50:350–355) Key Words: adrenal incidentaloma • cortisol • thyroid-stimulating hormone**

In healthy human volunteers, thyroid-stimulating hormone (TSH) secretion undergoes circadian variation, increasing during the late evening or early morning hours.[1–4] The measurement of the nocturnal serum TSH surge is a sensitive method that provides useful information on the central control of the hypothalamopituitary thyroid axis.[5–7] This test may show an impaired TSH secretion that may not be revealed by the evaluation of the circulating concentrations of TSH in the morning or by the measurement of the TSH response to thyrotropin-releasing hormone (TRH).

High blood cortisol levels of endogenous origin (Cushing's syndrome,[8] major depression,[9,10] and postsurgical conditions[11]) or produced by the administration of pharmacological doses of glucocorticoids[12] have been shown to be able to abolish the nocturnal serum TSH surge, which supports the well-known inhibitory role of glucocorticoids on TSH secretion. However, some indirect evidence (such as the observation that replacement therapy with glucocorticoids in Addison's disease is associated with decreased serum TSH levels[13]) has suggested that inhibitory effects on TSH secretion may be exerted by glucocorticoids even in conditions of slight excess. A possible experimental model to test this hypothesis may be the adrenal incidentaloma, an adrenal mass incidentally detected during imaging procedures carried out because of unrelated clinical problems.[14] Incidentalomas are not accompanied by clear laboratory evidence or clinical signs and symptoms of overt hypercortisolism; nevertheless, they are characterized by discontinuous derangement in the function of the hypothalamic-pituitary-adrenal axis.[14] Therefore, the endocrine condition associated with incidentaloma

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has been called preclinical or subclinical Cushing's syndrome, to underline the characteristic subtle hypercortisolemic activity of the adrenal mass.[15] However, at present, scant information exists about the effects of this slightly increased adrenal activity on other endocrine systems.

In this study, we evaluated the thyroid function in patients with incidentally discovered adrenal adenomas. The circadian variations of TSH surge, with particular regard to the nocturnal serum TSH surge, were measured in a group of patients with incidentaloma and in a group of normal controls. In addition, all subjects were tested with TRH.

MATERIALS AND METHODS

Patients

Eight consecutive patients (five men, three women; age range, 40–59 yr) with adrenal incidentalomas participated in the study. The diagnosis of adrenal incidentaloma was made on the basis of the incidental detection of an adrenal mass by diagnostic procedures performed for extra-adrenal complaints; imaging features typical for adrenal adenoma were observed in all patients. The inclusion criteria were as follows:

- Younger than 60 years of age
- Body mass index less than 30 kg/m^2
- Normal fasting glucose level
- Lack of signs and/or symptoms of hormonal hypersecretion
- No medication

No subjects had evidence of neoplastic disease. Patients with hypertension or possible signs of endocrine disease were excluded. Biochemical screening designed to exclude the presence of pheochromocytoma (measurement of 24-hour urinary excretion of catecholamines and vanillylmandelic acid) or aldosterone-producing adenoma (measurements of plasma renin activity and aldosterone in the recumbent position and after 3 hours of orthostatic posture were always performed). The diagnosis of adrenal adenoma was made after the assessment of imaging features of unenhanced computed tomographic (CT) scan and pattern of uptake at adrenal scintigraphy. At CT, all lesions were homogeneous and hypodense and had regular imaging. These features are comparable with the diagnosis of adrenocortical adenoma.[16]

Imaging

Adrenal scintigraphy showed a pattern of uptake concomitant with the CT scan.[17] Scintigrams with ^{131}I-6-iodomethyl-19-narcholet-5[10]-en-3-ol were obtained as described elsewhere.[18] All CT scans and scintigrams were reviewed by the same radiologist. All subjects volunteered to participate in the study and gave their informed consent. Ten healthy adult nonobese volunteers matched for age (control group age range, 37–58 yr) and body mass index with the above-described patients and not undergoing any therapy were used as controls. Premenopausal women were studied during the early follicular phase (Days 3–8) of the menstrual cycle. All subjects showed negative antithyroid antibodies (Ab). The circulating anti-TSH receptor Ab were evaluated by a radioreceptor binding assay with materials supplied by Radim (Pomezia, Italy), and thyroid peroxidase Ab were measured with materials obtained from Radim that used highly purified human thyroid peroxidase. None of the patients with adrenal incidentaloma and none of the control subjects were affected by major affective disorders as determined by the Hamilton Depressive Rating scale. In addition, all patients also underwent the following endocrine evaluation that aimed to study the hypothalamic pituitary adrenal axis:

- Measurements of the 24-hour excretion of urinary free cortisol (mean of at least two samples on different days).
- Measurement of plasma adrenocorticotropic hormone (ACTH) at 8:00 AM (mean of at least two samples on different days).
- Overnight low-dose dexamethasone suppression test (1 mg orally at 11:00 PM with measurement of serum cortisol at 8:00 AM the next morning). Adequate dexamethasone suppression was demonstrated when cortisol values fell below 5 μg/dL on the morning after dexamethasone administration. The same endocrine work-up was performed in the control subjects.

Study Design

Blood was drawn from all subjects at 30-minute intervals between 10:30 PM and 2:00 AM and between 8:00 and 8:30 AM. This procedure, although it did not allow the evaluation of change in amplitude and frequency, does provide a reasonable assessment of the overall nocturnal serum TSH surge. According to the method of Bartalena et al,[6,8,10,11] the morning value and the highest nighttime TSH value were compared; the nocturnal TSH peak was determined by dividing the difference between nighttime and morning TSH values by the morning TSH values and then multiplying by 100.

After the morning basal sampling, a TRH (200 μg) stimulation test was assessed by measuring serum TSH levels 30 minutes after TRH administration. Hormonal variables were measured by radioimmunoassay or immunoradiometric assay methods that used commercially available kits: serum TSH concentration was measured with a sensitive immunoradiometric assay. The sensitivity of the assay was 0.02 mU/L for TSH; the intra- and

interassay coefficients of variation for TSH were 4.8 and 6.7%, respectively. Serum free thyroxine (FT4) and serum free triiodothyronine (FT3) were measured by immunoradiometric assay.

Plasma ACTH and serum cortisol concentrations were measured by radioimmunoassay. The intra- and interassay coefficients of variation were 3.8 and 7.8% for ACTH and 4 and 7% for cortisol, respectively. The lower limit of sensitivity was 1.5 pg/mL for ACTH and 0.6 μg/dL for cortisol. The assay for urinary cortisol was performed as described for serum samples, with the use of the same standard curve. In our laboratory, the normal range of urinary cortisol values is 10 to 90 μg/24 h. All samples from the same subject were measured in the same assay, in duplicate and in random order. Data were analyzed statistically with a nonparametric analysis of variance (Kruskall-Wallis test) and paired or unpaired Student's *t* test, as appropriate. Data are reported as mean ± SEM.

RESULTS

Clinical and hormonal data of all subjects are summarized in the Table. According to selection criteria, urinary free cortisol levels were significantly higher in patients with incidentaloma ($P<0.01$). In addition, ACTH concentrations were significantly lower in patients with incidentaloma than in controls ($P<0.001$). After dexamethasone suppression, cortisol levels were not different between groups (Table).

Nocturnal serum TSH levels were significantly higher in the normal controls than in subjects with adrenal incidentaloma ($P<0.05$) (Figure 1). Figure 2 shows that the normal controls had a nocturnal TSH peak higher than that of patients with adrenal incidentaloma ($P<0.001$). On the next morning, TSH levels were significantly lower in the control group in comparison with the night TSH values ($P<0.002$). A slight but significant difference between

Table 1. Clinical and biochemical data.[a]

Patient no.	Age (yr)/Sex	Body mass index (kg/m^2)	Reason for imaging procedure	Mass size (cm)	ACTH (pg/mL)	UFC (μg/24 h)	F dex (mg/dL)
Experimental group							
1	59/M	26	Renal colic	1.8	14	67	1.8
2	56/M	22	Prostatitis	2.1	6.2	100	2.6
3	41/M	19	Abdominal pain	2.9	4.0	129	1.1
4	45/M	18	Renal colic	2.8	25	68	2.4
5	40/F	23	Medical screening	3.2	7.1	98	1.0
6	42/F	22	Biliary colic	1.7	2.9	46	1.8
7	50/F	21	Abdominal pain	2.5	9.0	92	1.6
8	49/M	24	Biliary colic	2.4	11.9	80	—
					13.2 ± 3.2	85 ± 9.0	1.7 ± 0.2
Control group							
1	58/M	25			28	45	1.0
2	37/M	21			34	49	1.0
3	39/F	20			27	38	1.8
4	42/M	25			20	72	1.6
5	43/F	22			17	78	1.2
6	50/F	23			38	52	1.0
7	46/M	24			29	59	1.9
8	44/M	21			34	43	1.5
9	52/F	23			39	55	2.0
10	45/M	20			42	35	1.5
					30.8‡‡ ± 2.6	52.6‡ ± 4.4	1.5 ± 0.2

[a]UFC, urinary free cortisol; F dex, cortisol after 1 mg dexamethasone; ACTH, adrenocorticotropic hormone.
‡$P < 0.01$ (UFC).
‡‡$P < 0.001$ (ACTH).

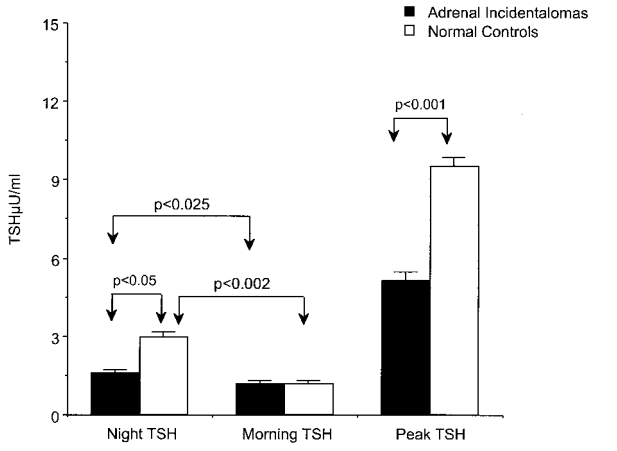

Figure 1. *Mean (±SE) serum TSH levels at night and in the morning and mean (±SE) TSH peak value after TRH injection in patients with adrenal incidentaloma and in normal controls.*

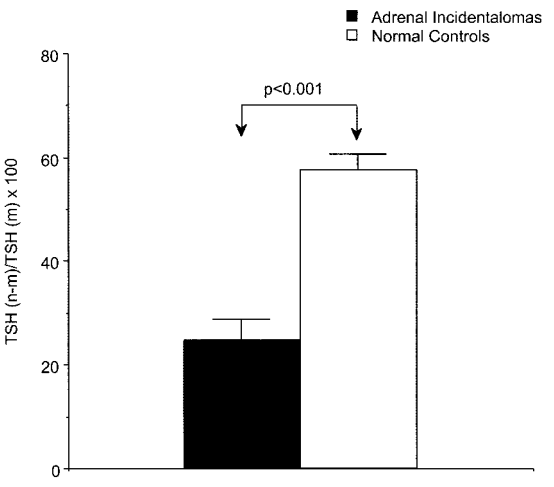

Figure 2. *Mean (±SE) nocturnal serum TSH peak in patients with adrenal incidentaloma and in normal controls.*

night and morning TSH values was also observed in the group with adrenal incidentaloma ($P<0.025$) (Figure 1). Comparison between groups did not show significant differences in the morning TSH levels. The mean TSH peak after TRH administration was significantly lower in the group with adrenal incidentaloma than in the normal controls ($P<0.001$) (Figure 1). Serum FT4 and FT3 were similar in patients with adrenal incidentaloma (FT4, 2.6±0.2 pg/mL and FT3, 1.4±0.1 ng/dL, respectively) and in normal controls (FT4, 2.8±0.2 pg/mL and FT3, 1.5±0.1 ng/dL, respectively).

DISCUSSION

The data reported herein show a reduction of the nocturnal TSH surge in subjects with incidentaloma, which suggests that, even in the presence of a slight cortisol excess, thyroid secretion is altered. TSH secretion is under the control of the stimulating action of endogenous TRH and the inhibitory effect of circulating thyroid hormone levels. An important role in the coordination of the hormone circadian rhythms is attributed to the suprachiasmatic nuclei.[19,20] Also for TSH, the major determinant of the circadian secretory rhythm is thought to be of central origin. In fact, animal studies have shown that the nycterohemeral rhythm of TSH is abolished by basal hypothalamic deafferentation.[19] However, modifications in serum thyroid hormone concentrations will influence the circadian pattern of TSH secretion.[11] Our findings argue against the possibility that an increased feedback inhibition by circulating thyroid hormone levels was responsible for the blunted night increase in serum TSH in patients with incidentaloma. In fact, we observed normal serum thyroid hormone concentrations in this group. The nocturnal TSH surge is a very sensitive test of the hypothalamic-pituitary control of the thyroid function (see introductory section). Our present finding of a defective TSH surge in patients with incidentaloma suggests the presence of a corticosteroid-dependent neuroendocrine dysfunction in the central nervous system.

The possibility of central hypothyroidism induced by slightly increased cortisolemic activity is supported by our additional experiments that tested the TSH response to TRH. In fact, despite normal circulating thyroid hormone levels, patients with adrenal incidentaloma showed significantly lower TSH responses than normal volunteers. In agreement with this hypothesis, blunted growth hormone (GH) responses to GH-releasing hormone have been reported not only in patients who have been chronically treated with pharmacological doses of glucocorticoids[21,22] but also in subjects with a slight cortisol excess due to incidental adenomas.[23] Of interest, in both experimental conditions, the administration of arginine restored a normal GH responsiveness to GH-releasing hormone, which suggests a possible role of somatostatin in the inhibitory activity of glucocorticoids on GH secretion,[23] because arginine is a well-known functional somatostatin antagonist.[24] An increased somatostatinergic tone is thought to be produced even by a very mild increase of glucocorticoids and in the absence of symptoms of hypercortisolism.[23] In our patients with incidentaloma, this condition may have been responsible for the slight but significant inhibition of TSH secretion unmasked by the lack of the nocturnal TSH surge. In fact, somatostatin is a well-known inhibitor of TSH secretion at the hypothalamic-pituitary level.[25,26]

CONCLUSION

These studies extend the number of observations of endocrine abnormalities in patients with adrenal incidentalomas and support the hypothesis that even conditions of slight glucocorticoid excess may exert inhibitory effects on TSH secretion.

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INVITED COMMENT

Thyrotropin (TSH) secretion shows a circadian rhythm, with a relevant surge during the late evening or early morning.[1] This pattern of secretion is under hypothalamic control, and the nocturnal TSH peak is abolished in patients with central hypothyroidism,[2,3] chronic renal failure,[4,5] and, in general, in severe nonthyroidal illnesses,[6] in untreated depression,[7] or after surgery.[8] Some of these conditions, especially untreated depression and surgical stress, are characterized by an activation of the hypothalamus-pituitary-adrenal gland axis that is responsible for some degree of hypercortisolism.

Indeed, glucocorticoids, not only at pharmacological doses but also at physiological doses, reduce TSH secretion in both humans[9] and animals.[10] In addition, correction of glucocorticoid deficiency, as in Addison's disease, is associated with a decrease in serum TSH concentration.[11] Therefore, it is not surprising that patients with marked hypercortisolism due to either adrenocorticotropin-dependent or

-independent overt Cushing's syndrome have a loss of the nocturnal serum TSH surge;[12] of interest, the abolishment of nocturnal serum TSH peak occurs before significant changes in TSH concentration become detectable in the morning.[12] In Cushing's syndrome, the loss of nighttime TSH peak is often associated with a reduction in serum free thyroid hormone levels.[12] Thus, overt hypercortisolism may be considered as a form of functional (and reversible) central hypothyroidism.[13] Very little is known about the effects of milder cortisol excess, as in subclinical Cushing's syndrome.

Incidentally detected adrenal masses (adrenal incidentalomas) are in most cases nonsecretory;[14,15] however, in a proportion of cases ranging from 9[14] to 24%,[15] subtle abnormalities have been reported of the hypothalamus-pituitary-adrenal gland axis that have been defined as subclinical Cushing's syndrome. It is a matter of argument whether this condition is really subclinical, because many of these patients have clinical features, such as obesity, hypertension, type 2 diabetes mellitus, and dyslipidemia, that are observed in overt hypercortisolism.[15] Assessment of extra-adrenal endocrine function in patients with adrenal incidentalomas has received little attention.

Coiro et al report, in a small cohort of patients with adrenal incidentalomas and subclinical Cushing's syndrome, that even a modest (i.e., "subclinical") cortisol excess may be associated with an impairment of TSH secretion, as assessed by the loss of the TSH nocturnal rise. Of interest, Coiro et al documented normal free thyroid hormone levels in their patients, which suggests that impairment of TSH secretion may occur at an early stage and precedes the changes in serum free thyroid hormone concentrations that are common in overt hypercortisolism. The fact that serum TSH concentrations in patients and controls did not differ confirms the higher sensitivity of the loss of nocturnal serum TSH peak in detecting an initial impairment of TSH secretion.

In summary, the interesting study by Coiro et al adds a novel piece of information on endocrine abnormalities found in adrenal incidentalomas, showing that this condition may be associated with slight (and marginally relevant) abnormalities of the pituitary-thyroid axis. In addition, it lends further support to the usefulness of nocturnal TSH peak assessment as a tool to unveil mild and initial abnormalities of TSH secretion.

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