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Voiding Dysfunction

Clinical Usefulness of Corticotropin Releasing Hormone Testing in Subclinical Cushing's Syndrome for Predicting Cortisol Replacement after Adrenalectomy

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Purpose: The purpose of this study was to investigate the clinical and hormonal features of patients with incidentally discovered adrenal adenomas in relation to corticotropin releasing hormone (CRH) testing and the clinical outcome of adrenalectomy.

Materials and Methods: Twenty-three consecutive patients with incidentally detected adrenal adenomas were included in this retrospective study. All the patients underwent abdominal computed tomography scans and hormonal assays, including assessment of circadian rhythms of plasma cortisol and corticotropin (adrenocorticotropic hormone, ACTH), a corticotropin stimulation test, and low-dose and high-dose dexamethasone tests. The patients were reevaluated at regular intervals (6, 12, and 24 months) for a median period of 24 months. Subclinical Cushing's syndrome (SCS) was diagnosed in patients with subtle hypercortisolism who did not present clinical signs of Cushing's syndrome.

Results: We calculated the responsive index (peak value of ACTH in CRH test/baseline value of ACTH in CRH test). Of 23 patients, 6 had Cushing's syndrome, 8 had SCS, and 9 had a non-functioning tumor. All patients underwent laparoscopic adrenalectomy. Several patients (5 of 6 with Cushing's syndrome and 2 of 8 with SCS) required cortisol replacement therapy after surgery. The remaining patients required no hormonal replacement after surgery. Those who required hormone replacement had a responsive index of less than 1.2. Those who did not need hormone replacement therapy had a responsive index of more than 2.0.

Conclusions: In our limited experience, the responsive index of the CRH test might be a valuable tool for predicting the need for cortisol replacement after surgery in patients with SCS.

Key Words: *Adrenalectomy; Corticotropin-releasing hormone; Cushing syndrome*

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INTRODUCTION

Subclinical Cushing's syndrome (SCS) is defined as autonomous cortisol secretion in patients who do not have the typical signs and symptoms of hypercortisolism. To screen for adrenal autonomy, an overnight dexamethasone (DEX) (1 mg) suppression test is currently recommended for patients with adrenal incidentaloma [1,2]. In a meta-analysis of 13 studies, including 2,005 patients with adrenal incidentalomas, autonomous cortisol secretion occurred in 5% of the patients [3]. Chronic, mild, endogenous cortisol excess in SCS patients may have important systemic effects on the human body. Although the obvious symptoms of Cushing's syndrome (CS) are absent, SCS patients have a higher risk of cardiovascular disease, obesity, diabetes mellitus, and osteoporosis [4-8]. Currently, there is no con-

sensus on the optimal management of SCS. Adrenalectomy may reduce the cardiovascular risk profile [8]; therefore, consideration of surgical treatment for younger patients and for those with disorders that may be attributed to autonomous glucocorticoid secretion may be reasonable. Patients with SCS should receive perioperative replacement of glucocorticoids because they are at risk for hypoadrenalism after removal of the functioning mass. They should be monitored for subsequent hypothalamic-pituitary-adrenal (HPA) axis recovery and clinical improvement [2,9]. However, guidelines for follow-up of those patients who have undergone resection have not been defined. The need for longer-term replacement and tapering of exogenous glucocorticoids has been assessed postoperatively in an empirical manner.

The corticotropin releasing hormone (CRH) test has been widely used as a noninvasive tool in the differential diagnosis of corticotropin (adrenocorticotropic hormone, ACTH)-dependent CS [10]. Following administration of CRH, most patients with pituitary-dependent CS show a rise in plasma ACTH and cortisol, usually to a peak level greater than that in normal subjects, whereas those with non-pituitary sources of ACTH do not. In typical CS with cortisol-producing adrenal adenomas, administration of CRH does not stimulate the production of ACTH. However, the response to the CRH test in SCS has not been reported. The purpose of the present study was to evaluate the presence of SCS in a group of consecutive patients with incidentally discovered adrenal adenomas and to examine whether the CRH test could predict the need for longer-term exogenous glucocorticoids after adrenalectomy.

MATERIALS AND METHODS

1. Patients

From 2003 to 2006, 23 consecutive patients (15 women and 8 men; age range, 20 to 72 years; mean, 51.5 years) with incidentally detected adrenal masses who were referred from several hospitals underwent laparoscopic adrenalectomy at Teikyo University Hospital. All incidentalomas were discovered by abdominal ultrasound or computed tomography (CT) scans performed for the evaluation of unrelated diseases or annual health checkups. None of the patients had extraadrenal malignancies, hypertension, or hyperglycemia of possible endocrine origin. No patient showed signs or symptoms of hormone production excess, and no patient was on any kind of hormonal therapy.

2. Preoperative evaluations

For blood chemistry and hormonal analyses, all patients were hospitalized 2 to 3 months before surgery to reduce the psychological stress that potentially alters the hormonal profiles. All patients underwent the following endocrine evaluation: baseline serum cortisol (F) and plasma ACTH at 0800, 1600, and 2400 hours (mean of at least 2 samples taken on different days); lutenizing hormone (LH), follicle stimulating hormone (FSH), and testosterone; and a low-dose 1-mg dexamethasone (DXM) suppression test (orally, 0.5 mg, twice a day for 2 days, with measurement of serum cortisol and other steroids at 0800 hours the following morning). Pheochromocytomas were excluded by measuring the 24-hour urinary excretion of catecholamines and vanillylmandelic acid. Plasma renin activity and serum levels of aldosterone in the upright posture were measured to exclude aldosterone-producing adenomas. The response of the pituitary-adrenal axis to exogenous CRH was assessed by using human CRH (100 μg intravenously at 0900). The serum levels of ACTH were measured before injection and at 15 minutes, 30 minutes, 60 minutes, and 90 minutes after injection. The responsive index was defined as the peak value of ACTH after injection/baseline ACTH value 100 (%). A high-dose DXM test was performed (2 mg, 4 times a day for 2 days) if the patient had not responded to the low-dose DXM suppression test. F circadian rhythm abnormalities were evaluated by calculating the F fraction as (F 2400/f 0800)×100. SCS was diagnosed according to the recommendations of the annual report of the research committee of "disorders of adrenal hormones" that is sponsored by the Ministry of Health and Welfare Japan [11]. The criteria, in addition to the presence of an adrenal mass and a lack of overt signs and symptoms of CS, for the diagnosis of SCS are as follows: 1) normal baseline of serum cortisol, 2) autonomy of cortisol secretion tested by 1 mg of DEX administration, 3) suppressed levels of plasma ACTH, 4) isotope uptake by the affected site of the adrenal gland, but not by the contralateral site as assessed by adrenal scintigraphy, 5) lack of diurnal rhythm of plasma cortisol levels, 6) low level of serum dehydroepiandrosterone-sulfate (DHEA-S), and 7) transient adrenal insufficiency or the atrophy of the residual normal adrenal after removal of the adrenal tumor. Conditions 1) and 2) are both essential with at least 1 additional positive finding for conditions 3) to 7) required for the diagnosis of SCS.

3. Laparoscopic adrenalectomy

All laparoscopic procedures were done with the patient under general anesthesia by use of the transperitoneal anterior approach as described elsewhere [12]. In a patient with bilateral asymmetric adrenal tumors, the adrenal gland with a dominant tumor was resected.

4. Postoperative follow-up

All patients were evaluated on the same schedule for a median period of 24 months. Serum levels of cortisol and ACTH were measured every 3 months. If clinical symptoms of cortisol deficiency were noted, an appropriate dose of cortisol was supplemented. A CRH test was done every 3 or 6 months. Abdominal CT scans were done 6 months and 12 months after the operation. None of the patients developed clinical signs of hormonal excess during the follow-up period. Women of reproductive age were studied in the early follicular phase of the menstrual cycle (days 3 to 6).

5. Corticoadrenal scintigraphy

Corticoadrenal scintigraphy was performed by using [^{75}Se]selenio-6α-methyl-19-nor-cholesterol (Scintadren, Amersham Pharmacia Biotech, Amersham, The Netherlands) in 14 patients. Scintigrams were obtained by crystal γ-camera 7 days after radiotracer injection. All scintiscans were reviewed by the same operator.

6. Endocrinological tests

All hormone assays were performed in the same laboratory by using commercially available kits. F was measured by a solid-phase chemiluminescent enzyme immunoassay and ACTH was tested by double-antibody ^{125}I radioimmunoassay.

7. Statistical analysis

Analysis of variance was used for comparison of mean hormone levels between groups. The nonparametric method (Mann-Whitney U-test) was used when the data were not distributed in a Gaussian manner. $p < 0.05$ was considered significant.

RESULTS

1. Clinical data

Patients (n=23; 8 men and 15 women; 20 to 72 years old; mean age, 51.5 years) with adrenal incidentaloma were included in this study (Table 1). In 10 patients, the tumors were located on the left side; in 13, they were on the right side. One patient presented with bilateral masses. According to the CT scans, the sizes of the tumors ranged from 2.6 to 140 ml. CS was diagnosed in 6 patients, SCS was diagnosed in 8, and nonfunctioning adrenal tumors were found in the other 9. The median tumor size was significantly larger in patients with nonfunctioning tumors than in patients with CS or SCS. All 6 CS patients, 6 of 8 SCS patients, and 3 of 9 nonfunctioning tumor patients were female. Three patients with CS and 2 patients with SCS had mild to severe hypertension, 2 patients with CS and 1 patient with SCS had type 2 diabetes with fasting hyperglycemia (>120 mg/dl), and 3 patients with CS, 4 patients with SCS, and 5 patients with nonfunctioning tumors were diffusely obese (body mass index>25).

2. Corticoadrenal scintigraphy

No uptake of radioisotope was seen in patients with a nonfunctioning tumor. Radioisotope uptake was bilateral and predominant on the left side in the 1 patient with a bilateral adrenal tumor (CS-5) and was asymmetrical and prevalent on the side of the lesion in 4 CS patients and 6 SCS patients.

3. Endocrine data

Mean baseline cortisol measured at 0900 was 24.4 μg/dl (range, 16.8 to 36.2 μg/dl) in the CS patients, 13.3 μg/dl (range, 9.1 to 18.6 μg/dl) in the SCS patients, and 12.4 μg/dl (range, 3.6 to 22 μg/dl) in the patients with non-functioning tumors. Baseline cortisol levels were significantly higher in the CS patients than in the patients with SCS or nonfunctioning tumors (p=0.02 and p=0.02, respectively). Circadian rhythm was not detected in any CS patients, but was noted in 2 of 8 SCS patients and in 1 of 8 patients with a non-functioning tumor. All patients with CS showed no suppression in either the low-dose (1 mg) or the high-dose (8 mg) DXM suppression tests. Low-dose DXM did not suppress serum cortisol levels in any patient with SCS. Low-dose DXM suppressed the serum cortisol levels in all patients with non-functioning tumors.

No response was observed in ACTH values with the CRH test in any CS patients. Of the 6 patients with SCS, 2 showed minor responses (responsive index, 1.0 and 1.2) and 4 showed higher responses to the CRH test (responsive index, 2.0 to 17.4). Patients with a nonfunctioning tumor showed responses to the CRH test with a responsive index between 2.8 and 8.5 (Table 1).

All patients underwent laparoscopic adrenalectomy. The histological diagnosis was cortical adenoma in all cases. After surgery, all CS patients and 2 SCS patients needed cortisol replacement therapy for adrenal insufficiency. The responsive indexes in their CRH tests were less than 1.2. The other 16 patients, whose responsive indexes varied between 2.0 and 17.4, did not require cortisol supplementation after the operation.

DISCUSSION

The term *adrenal incidentaloma* refers to an adrenal mass that is unexpectedly detected through an imaging procedure done for reasons *a priori* unrelated to adrenal dysfunction or suspected dysfunction [13]. Adrenal incidentalomas are typically detected during ultrasonography, CT scanning, or magnetic resonance imaging. Although these techniques permit a diagnosis without further evaluation, it is important to recognize that imaging results may not be definitive in any individual case. Surgery is the ultimate solution for the diagnostic-therapeutic dilemma of adrenal incidentaloma. However, there is insufficient evidence for the usefulness of surgical treatment in SCS patients to recommend it for all of them. Previous data about the effects of SCS and its natural history are still unclear. The problem is that the follow-up periods of such patients in various studies have been relatively short. For this reason, in our study, we estimated the tumor size by CT scan before surgery and surgical treatment was restricted to patients with larger tumors. Several reports suggest that 12 to 16% of patients with adrenal incidentaloma have some form of subclinical abnormalities in the HPA axis, designated as SCS [14-18]. Recent literature shows that patients with SCS may represent a population at higher risk for metabolic disorders and cardiovascular disease [4-8]. Laparoscopic surgery has made adrenalectomy a less invasive treatment, although the necessity for steroid supplementation could be a further burden for patients with adrenal incidentalomas. Patients with subclinical hypercortisolism should receive perioperative glucocorticoids because they are at risk for

TABLE 1. Patient characteristics and hormonal profiles

Patient	Age (sex)	BMI	Side	Tumor (L×W×H)	Tumor size (ml)	Abnormal uptake in adrenocortical scintigraphy	Baseline cortisol (0900 h) (mg/dl)	Circadian rhythm of cortisol secretion	Low dose dexamethason suppression test (DXM 1 mg)	High dose dexamethason suppression test DXM 8 mg	Responsive index in CRH test	Primary adrenal insufficiency post-op
CS-1	27 (F)	19.2	L	3.5×2.5×3.0	18.4	Yes (L)	16.8	Absent	Not suppressed	Not suppressed	N.C.	Yes
CS-2	20 (F)	25.1	R	3.0×2.0×2.0	6.0	Yes (R)	27.6	Absent	Not suppressed	Not suppressed	N.C.	Yes
CS-3	45 (F)	21.6	R	3.8×3.5×2.5	16.6	N.D.	36.2	Absent	Not suppressed	Not suppressed	N.C.	Yes
CS-4	33 (F)	32.0	L	3.0×3.0×1.8	8.1	Yes (L)	33.6	Absent	Not suppressed	Not suppressed	N.C.	Yes
CS-5	50 (F)	32.6	Bilateral	6.0×3.0×2.5	22.5	Yes (L)	17.2	Absent	Not suppressed	Not suppressed	N.C.	No
CS-6	46 (F)	21.2	L	5.0×4.0×2.2	22.0	Yes (L)	14.9	Absent	Not suppressed	Not suppressed	N.C.	Yes
SCS-1	46 (F)	23.2	R	5.0×4.5×2.0	22.5	Yes (R)	11.4	Normal	Not suppressed	N.D.	1.0	Yes
SCS-2	57 (F)	19.6	R	3.0×2.5×2.0	7.5	Yes (R)	10.9	Absent	Not suppressed	N.D.	1.2	Yes
SCS-3	67 (F)	26.0	L	3.4×2.7×2.3	10.6	Yes (L)	10.8	Normal	Not suppressed	Suppressed	6.6	No
SCS-4	67 (F)	28.9	L	4.0×1.5×1.3	3.9	No	18.4	Normal	Not suppressed	N.D.	17.4	No
SCS-5	60 (F)	28.4	L	3.5×3.0×2.5	13.1	Yes (L)	15.1	Normal	Not suppressed	Suppressed	4.8	No
SCS-6	69 (M)	21.6	R	4.0×2.0×2.0	8.0	N.D.	11.8	Normal	Not suppressed	Suppressed	2.5	No
SCS-7	72 (M)	23.9	R	3.8×2.8×2.4	17.8	Yes (R)	9.1	Absent	Not suppressed	N.D.	2.0	No
SCS-8	48 (F)	26.9	L	3.5×2.0×2.0	7.0	Yes (L)	18.6	Normal	Not suppressed	Suppressed	3.8	No
NFT-1	37 (F)	27.4	L	5.0×2.0×1.0	5.0	No	14.5	Normal	Suppressed	N.D.	4.8	No
NFT-2	40 (M)	24.3	R	8.0×5.0×2.0	40.0	N.D.	10.0	Normal	Suppressed	N.D.	2.8	No
NFT-3	65 (M)	26.9	L	2.0×1.5×2.5	3.8	No	22.0	Normal	Suppressed	N.D.	3.8	No
NFT-4	53 (M)	25.0	R	2.3×1.5×1.5	2.6	No	13.3	Normal	Suppressed	N.D.	7.2	No
NFT-5	52 (F)	26.1	R	8.0×6.0×5.0	120.0	N.D.	14.1	Absent	Suppressed	N.D.	4.8	No
NFT-6	55 (M)	23.2	L	5.0×3.0×3.0	22.5	N.D.	14.8	Normal	Suppressed	N.D.	4.1	No
NFT-7	67 (M)	24.3	R	10.0×7.0×4.0	140.0	N.D.	3.6	Normal	Suppressed	N.D.	8.5	No
NFT-8	50 (F)	27.2	R	9.0×6.0×2.0	54.0	N.D.	8.3	Normal	Suppressed	N.D.	3.0	No
NFT-9	58 (M)	24.7	R	6.0×4.0×2.7	32.0	No	11.0	Normal	Suppressed	N.D.	3.9	No

BMI, body mass index; DXM, dexamethasone; CRH, corticotropin releasing hormone; CS, Cushing syndrome; SCS, subclinical Cushing syndrome; NFT, non functioning tumor; L, left; R, right; N.D., no date; NC, not calculated.

hypoadrenalism after removal of the functioning mass. They should be monitored for subsequent HPA axis recovery and clinical improvement, which requires regular visits to the ambulatory clinic. Thus, the probability of necessary postoperative steroid supplementation should be explained at the time of obtaining informed consent for the operation. However, predicting which patients will need glucocorticoid replacement therapy after surgical treatment of the adrenal adenoma is not an easy task. Several lines of evidence suggest that radiocholesterol uptake reflects the functional characteristics of adrenocortical lesions. In a recent study, adrenal scintiscans were performed in 136 patients affected by adrenal incidentaloma, indicating a significant positive correlation between abnormalities in the cortisol secretion rate and radiotracer uptake [19]. However, Rossi et al. [6] argued that the scintigraphic pattern of the uptake of radiocholesterol is not effective for predicting adrenocortical insufficiency after surgical treatment. They demonstrated that preoperative abnormalities in cortisol production are not reliable in predicting which patients will need glucocorticoid replacement therapy after surgical treatment of the adenoma. Thus, they propose that all patients who undergo adrenalectomy should be screened for residual adrenal function [6].

The CRH test is in widespread use for the differential diagnosis of ACTH-dependent CS [10]. It is also useful for monitoring the postoperative restoration of the suppressed pituitary-adrenal function in CS [20].

In our limited experience, SCS patients whose responsive index was <2.0 required steroid supplementation after adrenalectomy. To our knowledge, this is the first report to show that the responsive index obtained by the preoperative CRH test could be used to predict the postoperative need for hormonal replacement in SCS. Further study is necessary to confirm the usefulness of this index.

CONCLUSIONS

The responsive index (peak value of ACTH in CRH test/baseline value of ACTH in CRH test) of the CRH test might be an effective tool for predicting the need for cortisol replacement after surgery in SCS patients.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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