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

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-
Incidentally detected adrenal masses who were referred 8 men; age range, 20 to 72 years; mean, 51.5 years) with
From 2003 to 2006, 23 consecutive patients (15 women and
1. Patients
MATERIALS AND METHODS
were hospitalized 2 to 3 months before surgery to reduce
For blood chemistry and hormonal analyses, all patients
2. Preoperative evaluations
and no patient was on any kind of hormonal therapy.
 ACTH at 0800, 1600, and 2400 hours (mean of at least 2
 All patients were evaluated on the same schedule for a me-
 transient adrenal insufficiency or the atrophy of the re-
 The purpose of the present study was to evaluate the pres-
 the response to the CRH test in SCS has not been reported.
 in incidentally discovered adrenal adenomas and to examine
 whether the CRH test could predict the need for lon-
 gland were referred from several hospitals underwent laparoscopic adrena-
 by calculating the F fraction as (F 2400/f 0800)×100. SCS was diagnosed according to the recommendations of
 annual report of the research committee of “disorders of adrenal hormones” that is sponsored by the Ministry of
 that CRH does not stimulate the production of ACTH. However,
 cortisol-producing adrenal adenomas, administration of
 The corticotropin releasing hormone (CRH) test has
 studies performed for the evaluation of un-
 from several hospitals underwent laparoscopic adrenalecto-
 All incidentalomas were discovered by abdominal ultrasound or computed to-
 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) sup-
 pressed levels of plasma ACTH, 4) isotope uptake by the
 affected site of the adrenal gland, but not by the con-
 tralateral 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 re-
 tional positive finding for conditions 3) to 7) required for the
diagnosis 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 au-
tonomous glucocorticoid secretion may be reasonable. Patients with SCS should receive perioperative replace-
ment of glucocorticoids because they are at risk for hypoa-
drenalism after removal of the functioning mass. They
should be monitored for subsequent hypothalamic-pitui-
tary-adrenal (HPA) axis recovery and clinical improve-
[][12]. In a patient with
3. Laparoscopic adrenalectomy
All laparoscopic procedures were done with the patient un-
der general anesthesia by use of the transperitoneal ante-
rior 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 me-
dian 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 corti-
sol 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 ear-
ly follicular phase of the menstrual cycle (days 3 to 6).
5. Corticoadrenal scintigraphy
Corticoadrenal scintigraphy was performed by using \[^{75}\text{Se} \text{Seleno-6a-methyl-19-nor-}
\text{cholesterol (Scintadren, Amersham Pharamcia Biotech, Amersham, The Netherlands) in 14 patients. Scintigrams were obtained by crystal \(\gamma\)-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 \(^{125}\text{I} \) 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 \(\mu\text{g/dl (range, 16.8 to 36.2 \(\mu\text{g/dl}) in the CS patients, 13.3 \(\mu\text{g/dl (range, 9.1 to 18.6 \(\mu\text{g/dl}) in the SCS patients, and 12.4 \(\mu\text{g/dl (range, 3.6 to 22 \(\mu\text{g/dl}) in the patients with nonfunctioning 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 nonfunctioning 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 nonfunctioning 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 \textit{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 size (L×W×H) | Adrenal uptake in scintigraphy | Baseline cortisol (0900 h) (mg/dl) | Circadian rhythm of cortisol secretion | Low dose dexamethasone suppression test DXM 1 mg | High dose dexamethasone 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)                           | 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                             | N.C.                           | Yes                                 |
| CS-3    | 45 (F)    | 21.6| R    | 3.8×3.5×2.5         | 16.6                         | N.D.                              | 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                             | 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                             | 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                             | 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                                |
| 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                                |
| 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                                |
| 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                               |
| 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                                |
| 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                                |
| 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                                |
| 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                                |
| NFT-1   | 37 (F)    | 27.4| L    | 5.0×2.0×1.0         | 5.0                          | No                                 | 14.5                                | Normal                                     | Suppressed                               | N.D.                           | 4.8                                |
| 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                                |
| NFT-3   | 65 (M)    | 26.9| L    | 2.0×1.5×2.5         | 3.8                          | No                                 | 22.0                                | Normal                                     | Suppressed                               | N.D.                           | 3.8                                |
| NFT-4   | 53 (M)    | 25.0| R    | 2.3×1.5×1.5         | 2.6                          | No                                 | 13.3                                | Normal                                     | Suppressed                               | N.D.                           | 7.2                                |
| 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                                |
| 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                                |
| 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                                |
| 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                                |
| NFT-9   | 58 (F)    | 24.7| R    | 6.0×4.0×2.7         | 32.0                         | No                                 | 11.0                                | Normal                                     | Suppressed                               | N.D.                           | 3.9                                |

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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