Serum Levels of Dehydroepiandrosterone Sulfate in Patients with Asymptomatic Cortisol Producing Adrenal Adenoma: Comparison with Adrenal Cushing's Syndrome and Non-Functional Adrenal Tumor

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Abstract. The reported number of adrenal incidentalomas has been increasing because of wider application of imaging techniques. Patients with asymptomatic cortisol producing adrenal adenoma (ASCA) which secretes cortisol without clinical evidence of Cushing's syndrome has been more frequently observed than previously assumed, and they have a risk of adrenal insufficiency after adrenalectomy. Therefore patients with incidentalomas should be screened for cortisol overproduction. The aim of this study is to discover an easy screening test to uncover ASCA. We investigated the hormone profiles of 4 patients with ASCA in comparison with 11 patients with non-functional adrenal tumor and 10 patients with adrenal Cushing's syndrome. We also investigated the expression of dehydroepiandrosterone sulfotransferase (DHEA-ST) in surgically removed attached non-neoplastic adrenal tissues by immunostaining, which was considered to represent the degree of suppression of the hypothalamo-pituitary-adrenal axis. Serum dehydroepiandrosterone sulfate (DHEA-S) levels of all the patients with ASCA and adrenal Cushing's syndrome were lower than those of healthy subjects of corresponding age, but they were within the normal range in the patients with non-functional adrenal tumors. The serum DHEA-S level reflects the degree of suppression of the normal adrenal gland by cortisol hypersecretion from adrenal tumors. But the serum level of DHEA-S decreases with age, and because the normal range of serum DHEA-S is low in elderly subjects, we should be careful to evaluate the level of DHEA-S in elderly patients with adrenal Cushing's syndrome or ASCA. The immunohistochemical study showed DHEA-ST expression was noticeably suppressed in the adjacent adrenal cortex in ASCA and adrenal Cushing's syndrome. The decreased expression of DHEA-ST may reflect autonomous neoplastic cortisol secretion and subsequent ACTH suppression in ASCA and adrenal Cushing's syndrome. A single measurement of plasma ACTH or measurement of ACTH response to corticotropin-releasing hormone was not enough to screen for ASCA because of the wide variation among the cases. Dexamethasone suppression test is essential in identifying ASCA and also a single determination of serum DHEA-S is easy and may be useful for the screening of ASCA in adrenal incidentalomas in young and middle aged subjects, and is especially useful for outpatients.

Key words: DHEA-S, Sulfotransferase, Adrenal tumor, Incidentaloma

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These so-called "adrenal incidentalomas" are usually asymptomatic and often classified as non-functional tumors, but in recent years there have been several case reports of asymptomatic cortisol producing adrenal adenoma (ASCA) which secretes cortisol without clinical evidence of Cushing's syndrome, the so-called "Pre-Cushing's syndrome" or "Preclinical Cushing's syndrome" [12–21]. Some cases with incidentaloma were reported to have had adrenocortical insufficiency after removal of the adrenal tumor [17, 20]. It is important to identify the subtle hyperfunctioning adrenal tumors before surgery. The aim of this study was to elucidate an easy, sensitive test for the screening of ASCA.

Serum dehydroepiandrosterone sulfate (DHEA-S) levels in the patients with adrenal Cushing's syndrome were significantly lower than those of healthy subjects [22, 23]. The serum DHEA-S decrease in adrenal Cushing's syndrome is due to ACTH decrease, because ACTH is a major regulator of androgen secretion from the adrenal cortex [24]. Plasma ACTH in ASCA was reported to be lowered by cortisol hypersecretion [12, 15, 17–21], and therefore a decrease in ACTH may lead to a DHEA-S decrease in ASCA.

We now report four cases of ASCA. Their hormone profiles were investigated in detail, and the serum levels of DHEA-S were compared with those in normal individuals, the patients with adrenal Cushing's syndrome and non-functional adrenal tumor.

To confirm cortisol hypersecretion by ASCA, atrophy of the adjacent adrenal cortex was identified by light microscopy with routine staining and immunostaining for dehydroepiandrosterone sulfotransferase (DHEA-ST). The expression of DHEA-ST in the attached non-neoplastic adrenal was considered to represent the degree of suppression of the hypothalamo-pituitary-adrenal axis [25].

### Patients and Methods

#### Subjects

Four patients with ASCA, (4 females, aged 42–66 yr, average 51.3 ± 9.5, mean ± SD) were studied. These patients were referred to our endocrine outpatient clinic from 1990 to 1994 for evaluation of incidentally discovered adrenal masses. The profiles of the patients are shown in Table 1.

The diagnosis of asymptomatic cortisol producing adrenal adenoma was substantiated on the basis of the following criteria: 1) no abnormal clinical signs of Cushing's syndrome. Hypertension (>160/95 mmHg), obesity (>120% of ideal weight), and noninsulin dependent diabetes mellitus (NIDDM) were not considered to be specific symptoms for Cushing's syndrome because they were frequently found in patients with adrenal incidentaloma [19];

#### Table 1. Endocrinological findings in the patients with asymptomatic cortisol producing adrenal adenoma (ASCA)

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age</th>
<th>Basal level of cortisol at 0800 h</th>
<th>Basal level of ACTH at 0800 h</th>
<th>Urinary cortisol excretion</th>
<th>Increase in response to CRH</th>
<th>Serum cortisol level after dexamethasone</th>
<th>Serum DHEA-S level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>µg/dl</td>
<td>µg/ml</td>
<td>µg/day</td>
<td>ACTH</td>
<td>1 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>10.8</td>
<td>2.1</td>
<td>216.8</td>
<td>3.9</td>
<td>0.0</td>
<td>N.D.</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>8.8</td>
<td>36.8</td>
<td>76.9</td>
<td>49.9</td>
<td>2.7</td>
<td>9.1</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>7.6</td>
<td>4.6</td>
<td>44.1</td>
<td>8.4</td>
<td>2.1</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>12.0</td>
<td>3.9</td>
<td>153.3</td>
<td>19.7</td>
<td>10.4</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

Normal range: 5–20 µg/dl, 10–52 µg/ml, 30–100 µg/day, >10 pg/ml, >5 µg/dl, <5 µg/dl, <3 µg/dl, ng/ml

N.D.: not done. Increase in response to CRH; Response to CRH was assessed in terms of the maximal increase in plasma ACTH and serum cortisol above the basal value. Maximal response was observed 30 min after CRH in cases 2 and 3, at 60 min in case 1, and at 90 min in case 4. Serum cortisol level after dexamethasone: 1 mg: 1 mg orally at 2300 h and measurement of serum cortisol at 0800 h the following morning. 2 mg and 8 mg: days 1 and 2, 0.5 mg four times a day; days 3 and 4, 2 mg four times a day; determination of serum cortisol level at 0800 h every morning. Serum sample for DHEA-S was obtained in the morning. Normal DHEA-S values vary with sex and age, and therefore normal values were shown in Fig. 1.
2) incidentally discovered adrenal mass; 3) normal serum cortisol levels (5–20 μg/dl) in the morning; 4) impaired suppressibility of plasma cortisol (not less than 5 μg/dl) caused by 1 mg dexamethasone administration; 5) lack of normal diurnal rhythm of serum cortisol (cortisol level over 5 μg/dl even at night); 6) unilateral uptake of 131I-6β-iodocholesterol-19-norcholest-5(10)-ene-3β-ol (131I-NCL) into the adrenal mass.

Twenty-one patients served as the controls. Of these, 10 patients suffered from adrenal Cushing’s syndrome (all females, aged 26–59 yr, average 43.1 ± 10.6) and 11 had non-functional adrenal tumor (7 males and 4 females, aged 29–78 yr, average 57.6 ± 14.1).

All the patients with adrenal Cushing’s syndrome had clinical features of hypercortisolism such as central obesity, moon face, buffalo hump and purple striae. The diagnosis of adrenal Cushing’s syndrome was established by means of standard tests of pituitary-adrenal function, including dexamethasone suppression tests.

A diagnosis of non-functional adrenal tumor was made on the basis of the following criteria: 1) an adrenal tumor was discovered incidentally; 2) no endocrinological abnormalities on clinical examination and no abnormal laboratory findings (normal serum cortisol level; normal serum aldosterone level; normal plasma renin activity; normal serum estradiol level and testosterone level; normal 24 hr urinary cortisol and catecholamine excretion; normal suppressibility of serum cortisol by 1 mg dexamethasone administration (<5 μg/dl)); 3) bilateral adrenal uptake of 131I-NCL.

Abdominal CT and 131I-NCL adrenal scan were performed in all the patients. A scintigram was taken with a gamma camera on day 7 after the intravenous injection of 37 MBq of 131I-NCL.

The diagnosis was confirmed by histopathological studies.

**Blood sampling, steroid assays and CRH test**

Blood samples were collected in the morning after overnight fasting. Serum and plasma samples were immediately separated by centrifugation at 4 °C. Twenty-four hour urine was collected for measurement of urinary free cortisol. Serum, plasma and urinary samples were stored at −20 °C until use.

Serum cortisol was measured by radioimmunoassay (RIA) with a commercial kit (Daiichi Radioisotope Labs., Ltd. Tokyo, Japan) and plasma ACTH was measured by immunoradiometric assay (IRMA) with a commercial kit (Mitsubishi Petrochemical Co., Ltd. Tokyo, Japan). Urinary free cortisol was measured by RIA with a commercial kit provided by Baxter Ltd. (Tokyo, Japan) at SRL Inc. (Tokyo, Japan).

Serum DHEA-S was directly measured by RIA with a commercial RIA kit provided by Nippon DPC Corporation (Chiba, Japan). The normal values for serum DHEA-S were obtained from 171 male and 124 female healthy subjects (male: 37 for 20–29 yr, 28 for 30–39 yr, 25 for 40–49 yr, 23 for 50–59 yr and 58 for older than 60 yr. Female: 31 for 20–29 yr, 18 for 30–39 yr, 18 for 40–49 yr, 14 for 50–59 yr and 43 for older than 60 yr) at Nippon DPC Corporation (Chiba, Japan). The normal value ranges are shown as 95% confidence limits in normal individuals.

The corticotropin releasing hormone (CRH) test was performed with an iv bolus injection of 100 μg CRH (human CRH, Peptide Institute Inc., Osaka, Japan) between 0800 and 1000 h. Blood samples were collected immediately before and 30, 60 and 120 min after the CRH injection. The maximal increases in plasma ACTH and serum cortisol concentrations from the basal level after CRH injection were calculated and are shown in Table 1.

**Pathology**

All surgically removed specimens were reviewed by one of the authors (H.S.). Light microscopic examination was performed on hematoxylin-eosin stained slides. Intraadrenal localization of DHEA-ST in the attached non-neoplastic adrenal cortex of the adenoma was examined for all the cases of ASCA, 2 cases of adrenal Cushing’s syndrome and 2 cases of non-functional adrenal tumor by immunostaining for DHEA-ST as previously reported [25].

**Statistical analysis**

The results are expressed as the mean ± SD. Statistical differences were determined by Scheffe’s F test. The level of statistical significance was set at \( P<0.05 \).
Case Report

Case 1

A 42-year-old woman was admitted to our hospital in March, 1994 for evaluation of a 2.5 x 1.5 cm tumor in her right adrenal gland. The tumor was discovered incidentally on an ultrasonic echography being performed for evaluation of fatty liver. She was diagnosed as having hypertension 16 years ago and since then an antihypertensive drug has been given. She was diagnosed as having diabetes mellitus 2 years ago, but it had been well controlled by diet therapy only.

Her body weight was 56.6 kg and height was 153.4 cm. Blood pressure was 142/96 mmHg without any drugs and the pulse rate was 82/min. She had a mild moon-face appearance, which, however, could only be identified retrospectively when this feature disappeared after the adrenalectomy. No other typical sign of Cushing's syndrome was seen.

Laboratory examination showed serum cortisol level to be normal at 0800 h but the diurnal rhythm of cortisol was lost (0800, 1200, 1600, 2000, 2400 and 0400 h; 10.0, 9.65, 9.92, 10.7, 11.52 and 10.26 µg/dl, respectively). The basal ACTH level was undetectable. The administration of dexamethasone did not suppress cortisol secretion, as shown in Table 1 (12.7 µg/dl after 2 mg and 16.2 µg/dl after 8 mg of dexamethasone). Neither ACTH nor cortisol responded to CRH injection. Urinary 17-OHCS, 17-KS and free cortisol excretion were 7.75 mg/day, 2.6 mg/day and 241.3 µg/day, respectively. Urinary catecholamine excretion was normal. 131I-NCL scintigraphy showed unilateral uptake on the right side.

In May, 1994 right adrenalectomy was performed. The histology of the tumor showed a benign adrenocortical adenoma, and the adjacent adrenal cortex was remarkably atrophied. After the adrenalectomy, the patient suffered from adrenal insufficiency, requiring replacement therapy with hydrocortisone. Blood pressure did not drop but hemoglobin A1c (HbA1c) decreased after the adrenalectomy (7.5% before the operation and 6.2% 6 months after).

Case 2

A 44-year old woman was admitted to our hospital in December, 1992 for evaluation of a 2.0 x 2.0 cm right adrenal tumor. The tumor was discovered incidentally on abdominal ultrasonography for a routine medical checkup. She had been taking an antihypertensive drug for 6 months. Her body weight was 59 kg and height was 164 cm. Blood pressure was 134/82 mmHg and her pulse rate was 64/min. The patient had no typical sign of Cushing's syndrome.

Endocrinological examination revealed a normal serum cortisol concentration at 0800 h but the diurnal rhythm was lost (0800, 1200, 1600, 2000, 2400 and 0400 h; 9.98, 8.81, 8.74, 7.93, 8.40 and 8.42 µg/dl, respectively). The basal ACTH level was normal (26.8 pg/ml) at 0800 h and the diurnal rhythm of ACTH was preserved. After 1 mg dexamethasone administration, the serum cortisol concentration was not suppressed (9.1 µg/dl after dexamethasone administration). ACTH responded to CRH injection but cortisol did not. Urinary 17-OHCS, 17-KS and free cortisol excretion were 3.7 mg/day, 4.4 mg/day and 76.9 µg/day, respectively. Urinary excretion of catecholamine was normal. 131I-NCL scintigraphy showed unilateral uptake on the right side.

In February, 1993 the right adrenal tumor was removed. Histology of the tumor showed a benign adrenocortical adenoma. The attached adrenal cortex was not examined. Hydrocortisone substitution was not necessary after the operation. Hypertension remained and the antihypertensive drug was continued after the operation.

Case 3

A 53-year-old woman was admitted to our hospital in November, 1992 for evaluation of a 1.9 x 1.0 cm right adrenal tumor. The tumor was discovered incidentally on a CT scan. She had been taking an antihypertensive drug for 3 years.

Her body weight was 50 kg and height was 146.5 cm. Blood pressure was 120/70 mmHg and the pulse rate was 88/min during admission. She showed no typical sign of Cushing's syndrome.

Endocrinological examination revealed a normal serum cortisol concentration but the diurnal rhythm
was lost (0800, 1200, 1600, 2000, 2400 and 0400 h; 10.46, 10.67, 6.23, 8.81, 6.23 and 7.61 µg/dl, respectively). Plasma ACTH was at an undetectable level at 0800 h. Oral administration of 2 mg and 8 mg of dexamethasone failed to suppress the serum cortisol level (7.3 µg/dl after 2 mg and 7.8 µg/dl after 8 mg of dexamethasone administration). Neither ACTH nor cortisol responded to CRH. Urinary 17-OHCS, 17-KS and free cortisol excretion were 2.5 mg/day, 2.0 mg/day and 46.9 µg/day, respectively. Urinary excretion of catecholamine was normal. 131I-NCL scintigraphy showed unilateral uptake on the right side.

In March, 1993 right adrenalectomy was performed. The histology of the tumor showed a benign adrenocortical adenoma. The adjacent attached adrenal cortex was thinned. Replacement of steroid hormone was not necessary. Her blood pressure was normal during admission but at the outpatient clinic an antihypertensive drug was considered necessary even after the operation.

Case 4

A 66-year-old woman was admitted to our hospital in May, 1991 for evaluation of a 2.8 x 2.2 cm left adrenal tumor. The tumor was discovered incidentally on a CT scan being performed for follow up of a liver hemangioma. She had been given an antihypertensive drug for 15 years. She was diagnosed as having diabetes mellitus 3 years previously by 75 g-oral glucose tolerance test (OGTT) and it was well controlled by diet alone. On physical examination the patient presented no typical signs of Cushing’s syndrome. Her body weight was 58 kg and height was 150 cm. Blood pressure was 160/94 mmHg and pulse rate was 74/min.

Endocrinological examination showed normal serum cortisol but the diurnal rhythm was lost (0800, 1200, 1600, 2000, 2400 and 0400 h; 14.83, 14.83, 15.39, 16.59, 13.4 and 14.19, respectively). Plasma ACTH was low (7.8 pg/ml) at 0800 h. After 2 mg or 8 mg of dexamethasone administration, the serum cortisol level was not completely suppressed (13.9 µg/dl after 2 mg and 12.0 µg/dl after 8 mg). Both ACTH and cortisol increased after CRH injection. Urinary 17-OHCS, 17-KS and free cortisol excretion were 6.2 mg/day, 4.1 mg/day and 149 µg/day, respectively. Other hormone levels including urinary catecholamine excretion were normal. 131I-NCL scintigraphy showed unilateral uptake on the left side.

In September, 1991 left adrenalectomy was performed. The histology of the tumor showed a benign adrenocortical adenoma. The attached adrenal cortex was thinned and cortical cells in this part showed signs of mild atrophy. After the adrenalectomy, the patient suffered from adrenal insufficiency, requiring replacement therapy with hydrocortisone. Blood pressure did not drop but HbA1C decreased after the adrenalectomy (6.3% before the operation and 5.6% 1 month after).

Results

The endocrinological findings for the patients with ASCA are summarized in Table 1. The serum cortisol level was normal in all of them, but not suppressed by dexamethasone administration. In 3 of 4 patients plasma ACTH was low, but normal in one patient (case 2). In two of four patients (cases 1 and 3), no ACTH response to CRH was observed, but in 2 other cases (cases 2 and 4) ACTH response was normal. Twenty-four hour urinary free cortisol excretion was normal in cases 2 and 3, but slightly increased in cases 1 and 4. Serum DHEA-S was low in all the patients with ASCA (Fig. 1).

Table 2 shows the clinical data for the patients with ASCA, adrenal Cushing’s syndrome and non-functional adrenal tumor. The patients with ASCA were younger than those with non-functional adrenal tumor and older than those with adrenal Cushing’s syndrome, but the difference was not significant. There was no significant difference among three groups in tumor size. Serum cortisol and urinary free cortisol levels in the patients with ASCA were similar to those in the patients with non-functional adrenal tumor and significantly lower than those in the patients with adrenal Cushing’s syndrome. The plasma ACTH level in ASCA was slightly higher than that in adrenal Cushing’s syndrome and lower than that in non-functional adrenal tumor, but the difference was not significant. Figure 1 shows the serum concentrations of DHEA-S in the patients with ASCA, adrenal Cushing’s syndrome and non-functional adrenal tumors with reference to the sex and age of each patient. Compared with healthy subjects and the patients of corresponding age with non-functional adrenal
tumors, serum DHEA-S levels were low in all the patients with ASCA (range; 45.2 to 190.0 ng/ml, 103.3 ± 59.9, mean ± SD) and Cushing's syndrome. All the patients with ASCA underwent unilateral adrenalectomy. In all cases the histology of the tumors showed benign adrenocortical adenoma. Atrophy of the adjacent adrenal cortex was noted in all the cases examined (3 cases, see “case report”). Figure 2 shows representative DHEA-ST immunoreactivity in normal adrenal (A), adjacent non-neoplastic adrenal cortex of adenoma of Cushing's syndrome (B), ASCA (C) and non-functional adrenal adenoma (D). In the attached adrenal in adrenal Cushing's syndrome, DHEA-ST expression was not observed or was very weak and only sporadically detected, as previously reported [25]. In the attached adrenal in ASCA (Case 4), DHEA-ST expression was weak and only sporadically detected. In the adjacent adrenal cortex in non-functional adrenal tumor, DHEA-ST expression was detected and the relative immunointensity was the same as in the normal adrenal.

The changes in serum DHEA-S, cortisol and plasma ACTH concentrations in the patients with ASCA after removal of the adrenal tumor are shown in Fig. 3. Although preoperative serum cortisol levels were normal in all the patients with ASCA, they decreased after adrenalectomy in two
patients (cases 1 and 4) but did not change in the other two patients (cases 2 and 3). The serum cortisol level returned to normal in case 4 within 9 months after the operation but it remained low in case 1 until 9 months after the operation. In three cases of ASCA (cases 1, 3 and 4), plasma ACTH levels were low before the operation but quickly returned to normal within 1-3 months after the operation. In case 2, the preoperative plasma ACTH concentration was normal but it rose beyond the normal range after the operation. The preoperative serum DHEA-S level was low in all the patients with ASCA. In two of them (cases 3 and 4), it increased gradually and returned to normal within one year after removal of the adrenal tumors. On the other hand, it still remained low in the other two patients at the end of this study (case 1, 9 months after the operation, and case 2, 19 months after the operation).

**Discussion**

Detailed endocrine tests revealed endocrine abnormalities in a considerable number of patients with incidentalomas, although a majority of incidentalomas have been reported to be nonfunctional after routine endocrine tests based on the measurement of basal adrenal hormones.

The present study revealed that serum levels of DHEA-S were low in the patients with ASCA and adrenal Cushing's syndrome [22, 23]. ACTH is a major regulator of androgen secretion from the adrenal cortex [24]. Androgen secreting adrenal cells are sensitive to the lack of ACTH stimulation [22, 26, 27] and therefore suppressed ACTH release in adrenal Cushing's syndrome results in decreased DHEA-S secretion. Furthermore DHEA-S levels remain low for a longer period than cortisol after recovery of ACTH secretion following remov-
The immunohistochemical study showed DHEA-ST expression was noticeably suppressed in the adrenal cortex adjacent to adenomas of adrenal Cushing’s syndrome and ASCA. It was reported that DHEA-ST expression in the zona reticularis cells of attached non-neoplastic adrenal glands of adrenocortical adenoma was considered to represent the degree of the suppression of hypothalamo-pituitary-adrenal axis [25]. The decreased expression of DHEA-ST in attached adrenal of ASCA may therefore reflect the autonomous neoplastic cortisol secretion and subsequent ACTH suppression in ASCA and adrenal Cushing’s syndrome.

The basal cortisol level in the morning was normal in the patients with ASCA but the plasma ACTH level was lower than in healthy subjects and slightly higher than in the patients with Cushing’s syndrome. In almost all of the patients with Cushing’s syndrome, the basal plasma ACTH level was undetectable by high sensitive IRMA assay, and in two cases examined ACTH and cortisol did not respond to CRH. Three of 4 patients with ASCA showed suppressed basal ACTH, but one showed normal ACTH. Two showed a rise in ACTH and cortisol levels after CRH. In case 2, the preoperative plasma ACTH level was 26.8 pg/ml which was within the normal range but might have been slightly suppressed because the plasma ACTH level was increased to 167.7 pg/ml one month after the operation (the serum cortisol level was 8.6 μg/dl at this time). In all the patients with non-functional adrenal tumor, plasma ACTH and serum cortisol levels were normal and, furthermore, in three cases examined, ACTH and cortisol showed a normal response to CRH. The ACTH level in patients with ASCA was reported to be suppressed [12, 15, 17-21], but in some other cases it was normal [13, 20, 21]. Thus the plasma ACTH levels varied among the patients with ASCA. This may be explained by the various amounts and duration of cortisol secretion by such tumors. Cortisol hypersecretion by the tumor may initially result in

Fig. 3. The change in serum DHEA-S (○), cortisol (●) and plasma ACTH (×) in the patients with ASCA after removal of the adrenal tumor. The shaded area represents the 95% confidence limits of serum DHEA-S levels in normal individuals. Upper left, case 1; upper right, case 2; lower left, case 3; lower right, case 4.
DHEA-S IN ADRENAL TUMOR

blunting the diurnal rhythm of cortisol and a lack of suppression of cortisol by dexamethasone. As ACTH is suppressed to lower levels, the response of ACTH and cortisol to CRH would progressively worsen [20].

Reincke et al. reported that the overnight dexamethasone suppression test was the best screening test for the ASCA in patients with incidentalomas [20]. Our results, in which all the patients with ASCA showed an abnormal response to dexamethasone, are in agreement with his report. The determination of diurnal cortisol secretion is of limited value in the evaluation of patients with ASCA, because the results may be difficult to interpret if cortisol production is low and evening cortisol levels are only slightly increased, and it is not practical for outpatients. The response of ACTH to CRH may be useful in identifying ASCA but there are limitations mainly due to the wide scattering of responses, resulting in difficulty in defining the normal response.

In 2 of 4 patients of ASCA, DHEA-S levels returned to normal within 12 months after removal of the adrenal adenoma. In 2 patients, hydrocortisone replacement was not necessary after removal of the adrenal adenoma. In Cushing's syndrome it takes longer for serum DHEA-S to return to normal [22]. Although atrophy of the residual adrenal cortex was noted in all the ASCA cases, these data suggested that suppression of the normal adrenal gland was weaker in the patients with ASCA than in those with Cushing's syndrome, and furthermore the DHEA-S level closely reflected the degree of suppression of the hypothalamo-pituitary-adrenal axis. DHEA-S may be a good indicator to predict the risks in postoperative adrenal insufficiency. Furthermore DHEA-S did not show a diurnal rhythm [28, 29] and therefore we can evaluate DHEA-S at any time.

In some reports, serum levels of DHEA-S were low in the patients with ASCA [15, 19, 21, 30, 31]. But in these reports, DHEA-S levels were not fully discussed compared with age matched controls. It has been reported that serum levels of DHEA-S decrease with age [22, 23]. As shown in Fig. 1, the normal range of serum DHEA-S gradually decreases and is low in elderly subjects. We should be careful to determine whether DHEA-S is normal or decreased in the elderly subjects.

On the basis of these results, we conclude that dexamethasone suppression test is essential in identifying ASCA and also that a single determination of serum DHEA-S levels is easy and may be useful for the screening of ASCA in young and middle aged subjects with adrenal incidentalomas and is especially useful for outpatients.

References


