The Evaluation of Clinical and Hormonal Parameters in the Prediction of Adrenocortical Carcinoma: Is DHEAS level a reliable marker of adrenocortical carcinoma?

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Adrenocortical carcinoma (ACC) is a rare malignant tumor which is more common in women and hirsutism may be an early sign of the disease. High DHEAS level is considered as the hallmark of the disease. In this study we have evaluated the hormonal and some of the clinical features of four women with ACC. Three patients had rapid onset hirsutism, all had hypokalemia and remarkably high serum 11-deoxycortisol levels associated with high testosterone levels. On the other hand 2 patients had normal serum DHEAS levels and one patient interestingly had dexamethasone suppressible DHEAS level. Only patients with high 17-hydroxyprogesterone level had increased DHEAS level which indicates steroidogenic defect is not uniform in patients with ACC. Also, we think that 11-deoxycortisol level may be more important than DHEAS level in the prediction of ACC.

Key words: Hirsutism, Adrenal cancer, DHEAS level

Introduction

Adrenocortical carcinoma (ACC) is a rare malignant tumour with a poor prognosis. Although malignant tumours as small as 2.5 cm in diameter have been reported, the size of the tumor may be an important feature of malignancy (1). These tumours are more common in women and hirsutism may be an early sign of ACC (1,2) which is a common endocrinological problem of the women, particularly in the childbearing age. Virilizing adrenocortical tumour is an uncommon cause of hirsutism and the extent to which hirsute women should be evaluated to exclude the likelihood of a virilizing tumour is still controversial (2,3). As well as the differential diagnosis of hirsutism, the differentiation between ACC and adenoma is also important. It has been suggested that ACC secretes significantly larger amounts of adrenal androgens (particularly DHEAS) that increased DHEAS may be a hallmark of ACC (4).

In this paper we report the results of endocrinological abnormalities of ACC in 4 patients with striking features of the disease.

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Patients and Methods

In the present study we have evaluated the hormonal and some of the clinical features of four women with ACC. Three women were admitted to the Hospital because of hirsutism and one woman was diagnosed as adrenal incidentaloma. Three patients (except case 3) were suffering from a rapid (within six months) onset of hirsutism and amenorrhea. Case 3, who was the youngest, had two years history of hirsutism and oligomenorrhea. This medical history suggested polycystic ovary syndrome and her right adrenal mass lesion was diagnosed as an adrenal incidentaloma. Abdominal and pelvic radiological examinations were performed by ultrasonography and computerized tomography in all patients. Additional examinations such as chest X-ray for the investigation of metastases were also performed. After having blood samples for biochemical and hormonal analyses with occasional dynamic tests, including dexamethasone suppression test, all the patients underwent surgical intervention for the histopathological diagnosis and the treatment of the mass lesion. The tumor was completely removed in two patients (Case 2 and 3), one with systemic metastasis.

The histologic criteria of malignancy were as follows; weight more than 100 g, lobulation, tumor cell necrosis, hemorrhage, mitotic activity, nuclear polymorphism, capsular lymph nodes and vascular invasion. After the confirmation of the diagnosis the patients were prescribed mitotane as an adjuvant therapy.

Results

The mean age of the patients was 42.2 (19-70) years. The main complaint of the patients was hirsutism. At diagnosis three patients with distant metastases (liver and lung) had features of Cushing's syndrome such as easy bruisinng, striae cutis and hypertension. None of the patients had virilizing signs such as excessive muscle mass, deepining of the voice and clitoromegaly. One of the patients had newly-diagnosed diabetes mellitus whose insulin requirement completely disappeared shortly after the surgical therapy. All the patients have normal blood chemistry except hypokalemia (< 3.6 mmol/L). Basal hormonal values are shown in Table 1. They are summarized as follows; very low levels of gonadotropins even in a postmenopausal woman (Case 4), remarkably high 11-deoxycortisol (11-S), androstenedione and testosterone levels. DHEAS levels were within normal limits in 2 patients. 17 hydroxyprogesterone (17-OHP) levels were silightly increased in patients with normal DHEAS levels but they increased several fold in the patients with high DHEAS levels.

None of the patients had suppressible cortisol levels after either low or high dose dexamethasone suppression tests. It is notable that one of the patients with high DHEAS level (Case 1) had suppressible DHEAS levels after high dose dexamethasone suppression test (Table 2).

Patients were prescribed mitotane for the adjuvant therapy of ACC. Except case 3, all took 4 g/day of mitotane. Case 3 was prescribed 2 g/day for 3 months

Table 1. Basal hormone values of the patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Normal
FSH (mIU/ml)	0.02	5.7	0.8	2.5	1.2-12.5
LH (mIU/ml)	0.1	3.4	0.1	1.7	2.5-10.2
Estradiol (pg/ml)	481.9	109	0.8	130	11-165
Cortisol (µg/dl)	118.7	46	69	22	9-26
17-OHP (ng/ml)	22.2	2.6	2	22.9	0.1-0.8
11-S (ng/dl)	11.8	8.3	9.3	23.5	< 8
SHBG (nmol/L)	19.5	35	40	22	20-140
DHEAS (ng/ml)	29841	1077	2788	7834	100-3300
Androstenedione (ng/ml)	40	6.9	5.3	5.8	0.4-2.7
T.Testosterone (ng/dl)	943	171	150	258	7-65
F. Testosterone (pg/dl)	24.4	12.1	5.8	15.5	0.3-3.1

11-S : 11-deoxycortisol ; 17-OHP: 17-hydroxyprogesterone

Table 2. Result of high dose (8mg/day) dexamethasone suppression test in Patient 1.

	Basal	48th hour
Cortisol (µg/dl)	118	104
17-OHP (ng/ml)	22.3	27
11-deoxycortisol (ng/ml)	21.5	23.5
DHEAS (ng/ml)	16129	111
Androstenedione (ng/ml)	40	41

and then 1 g/day of mitotane therapy. She is still free of symptom for 18 months, however the other patients died around 8 months of their therapy.

Discussion

Adrenocortical carcinoma is a rare tumour with an incidence of approximately 0,5-2 cases per million per year. Benign and malignant lesions cannot be reliably discriminated with CT and MR on the basis of radiological features and the distinction between benign and malignant tumours of adrenal gland is usually made after careful consideration of clinical evaluation and macroscopic and histo-pathologic examinations of the tumor tissue (1,5). ACC may be functional or non-functional and the most usual presentation of ACC is Cushing's syndrome or virilization syndromes (6,7). Except the third patient, all the patients had some signs and symptoms of Cushing's syndrome but not virilization syndromes. Virilization occurs in 20-30% of adults with ACC and it is secondary to hypersecretion of adrenal androgens. The main complaint of the patients was hirsutism and the absence of full blown Cushing's syndrome and virilization syndromes may be due to the relatively short medical history of the patients.

Several reports suggest that high serum adrenal androgens such as DHEAS and increased excretion of 17-KS indicate the presence of adrenocortical malignancy (8,9,10) and in vitro, it has been shown that ACC cells secrete more DHEA, DHEAS and androstenedione in comparison with adrenal adenoma (4). Derksen et al (2) suggest the importance of DHEAS levels in conjuction with testosterone levels, either basally or after dexamethasone suppression test, in the diagnosis of ACC. However, our two patients showed normal basal DHEAS levels and the first patient with very high basal DHEAS level showed a remarkable suppression after high-dose

dexamethasone suppression test. We think that the assay of DHEAS is not always very helpful for routine investigation of ACC in women with hirsutism. Similar suggestions have been reported recently (11).

Apart from a new-onset diabetes mellitus, the only biochemical abnormality was hypokalemia in these patients. Except one patient (third case has no data) all patients showed normal plasma renin activity and aldosterone levels and since there is no other obvious reason, we think that hypokalemia is the result of the mineralocorticoid activity of excess glucocorticoids. Additionally these patients showed severe new-onset hirsutism which is one of the important marker of androgen secreting tumours. Although hormonal prognostic factors should be considered cautiously, it has been suggested that corticosteroid secreting tumours, in comparison to non-secreting tumours or precursor secreting tumours, had less favorable prognosis (6). Precursor hormones such as 17-OHP and 11-S were remarkably high in these patients. It has been reported that women with hirsutism and ACC may have derangements of more than one steroidogenic pathway (2). Steroidogenic enzyme activities such as 11- hydroxylase and 21-hydroxylase may be deficient (4) and this in turn leads to the secretion of large amounts of steroid precursors and adrenal androgens (12).

ACTH stimulated 11-S levels are important biochemical parameters for the diagnosis of non-classic congenital adrenal hyperplasia due to 11- hydroxylase deficiency (13). The result of this study show that high 11-S level (both basal and ACTH stimulated) is also an important marker of ACC. Besides the androgen levels, 11-S level is notably high in all patients so, 11-S may be more valuable than DHEAS levels in terms of the ACC prediction in women with new-onset hirsutism and adrenall mass lesion. Although the number of patients in this study is limited, 50% of the patients have normal DHEAS levels. Midorikawa et al (4) showed that in vitro studies of steroidogenic enzymes demonstrated a lower activity of 21-hydroxylase activity in adrenal carcinoma tissue and they suggest that the adrenal carcinoma tissue may predominantly synthesize adrenal androgens because of the relative deficiency of 21-hydroxylase. Our results confirm this in vitro

results since patients with remarkably increased 17 OHP levels (which is an indicator of 21-hydroxylase deficiency) have increased DHEAS levels.

In a recent paper by Luton et al. (11) 16% of the adrenal incidentalomas were malignant tumours and 2% were ACC. They report that malignancy was associated with weight loss and increased tumour size. The third patient had actually an adrenal incidentaloma diagnosed on abdominal USG which was evaluated only because of right side abdominal discomfort. It is noteworhy that, in contrary to the new-onset severe hirsutism, the clinical history of the third patient was compatible with polycystic ovary syndrome (PCOS). This patient had a relatively long medical history and in contrast to other patients, although endocrinological tests established Cushing's syndrome, she had no sign of the disease. The patient was considered as having subclinical Cushing's syndrome. Subclinical Cushing's syndrome has been defined as autonomous cortisol secretion but not associated with any specific signs of Cushing's syndrome.

The differentiation of benign from malignant adrenocortical neoplasms solely on the basis of histological finding is difficult and it has been reported that patients with histologically benign disease have subsequently developed metastases while the patient with microscopic appearence of malignancy live tumor-free for many years (12). The third patient is an interesting example of this suggestion since she is completely well with the lowest dose of mitotane. Surgical therapy is the most effective way to cure and prolong the survival rates in patients with ACC, particularly in the early stages of the disease (12). Although mitotane is one of the most important agent currently employed for the treatment of ACC (14,15) its role in the treatment of ACC is controversial (12,16,17,18,19). Recently, lower doses of mitotane have been used with various success rates and limited unwanted effects (20). It has been suggested that low-dose mitotane treatment has to be started very shortly after the surgery and the lowest dose we met in the English literature was 1.5 g/day (16). In the third patient we used very low dose (1 g/day) mitotane since the tumour was confined to the adrenal gland and had no metastasis. The patient was symptom free at 18 months of the disease. Therefore it can be speculated that this case is low grade malignancy and she is still alive without any metastasis and with the lowest dose of mitotane.

In conclusion, like its various histopathologic features, the clinical manifestations of ACC is quiet different in women with ACC. Hirsutism and signs of Cushing's syndrome are the most important finding in women and some steroid precursors (particularly 11-S) compaired to DHEAS levels may be more important in the prediction of ACC.

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