Case Report
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ADRENAL ANDROGEN PRODUCING ADENOMA ASSOCIATED WITH EPILEPTIC SEIZURES

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Abstract

Background. Dehydroepiandrosterone sulphate (DHEA-S) is a major steroid product of adrenal glands and an important neurosteroid, but due to only slight androgenic activities pathology of DHEA-S secretion it was rarely described until now.

Aim. To report a case of DHEA-S and testosterone secreting adrenal tumour with clinical manifestations of suddenly appeared epileptic seizures, amenorrhea, hirsutism, weight gain and decreased sexual activity before operation, and up to 12 months observation after surgical removal of the tumour.

Methods. Presentation of clinical case with comments.

Results. Epileptic seizures, amenorrhea, weight gain and hirsutism suddenly appeared in a 38-year-old fertile woman. A right adrenal tumour was detected. Blood levels of DHEA-S and testosterone were very high. Surgical removal of the adenoma (confirmed histologically) was performed what conditioned decrease of DHEA-S, testosterone and other hormones in 2-24 hours for the level of adrenal insufficiency. After a month all the hormones returned to normal level and were maintained at this level for 12 months after operation, excepting aldosterone, which increased gradually. Menses reappeared in six weeks after a short period of hot flashes and perspirations. Seizures did not appear in 12 months. Sexual activity was lowered one month before and after the operation, and it was maximal 6-12 months after operation.

Conclusions. We report a case with complete recovery of a 38-year-old woman, presented with epileptic seizures, amenorrhea, hirsutism, weight gain and decrease of sexual activity, before and after surgical removal of DHEA-S and testosterone secreting adrenal tumour.

Key words: Dehydroepiandrosterone sulphate, testosterone, adrenocortical oncocytoma, seizures, sexuality.

INTRODUCTION

Modern medical visual technologies made a new group of diseases to be born – incidentalomas. Tumoural masses incidentally found in adrenal regions are considered to be adrenal incidentaloma (1-4). About 85% of adrenal incidentalo-

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mas are non-secretory. Secretory adrenal incidentalomas in decreasing order of frequency are these secreting glucocorticoids (subclinical Cushing's disease), mineralocorticoids (hyperaldosteronism, Conn's disease), and catecholamins (pheochromocytoma).

Although DHEA-S is a major product of adrenal secretion, DHEA-S secreting tumours are rarely described and their clinical manifestations are not clearly defined. Traditionally, high levels of DHEA-S in adrenal incidentalomas are considered to be a sign of malignancy of the tumour. On the contrary, low to low-normal values of DHEA-S are characteristics of benign tumours – adrenal adenomas (2).

The peculiarity of the presented case is that DHEA-S and testosterone secreting tumour is described in a woman of normal reproductive health period with a sudden development of clinical symptoms: epileptic seizures, amenorrhea (secondary, hypogonadotropic), weight gain, hirsutism and decrease of sexual activity. The patient completely recovered after removal of adrenal tumour.

SUBJECT AND METHODS

Case presentation

A 38-year-old woman was referred to the university clinics with a diagnosis of hypogonadotropic hypogonadism, amenorrhea, weight gain and epileptic seizures. She complained about secondary amenorrhea lasting 8 months, weight gain (23 kg in 6 months), hirsutism and 3 episodes of tonic-clonic seizures. Her blood pressure was normal 110/80 mmHg and so was glycaemia 5.07 mmol/L. Before and after the surgery patient did not receive any hormonal treatment.

Large 6-8cm right adrenal tumour was detected by ultrasound. Computed tomography confirmed the presence of a 5.8 x 4.6 cm right adrenal tumour, which was oval-shaped, with homogeneous content and well-defined margins and suspected to be pheochromocytoma by a radiologist (Fig. 1).

All the hormone levels before and 2, 24 hours and one, 3, 6, 12 months after the surgery are presented in Table 1. Before the surgery LH and FSH were decreased (resulting with secondary hypogonadotropic amenorrhea), prolactin, metanephrine, normetanephrine, renin, cortisol, ACTH and estradiol were at normal level, aldosterone and 17-OH progesterone – slightly increased, but DHEA-S and testosterone –highly increased. Brain MRI and sleep EEG were negative.

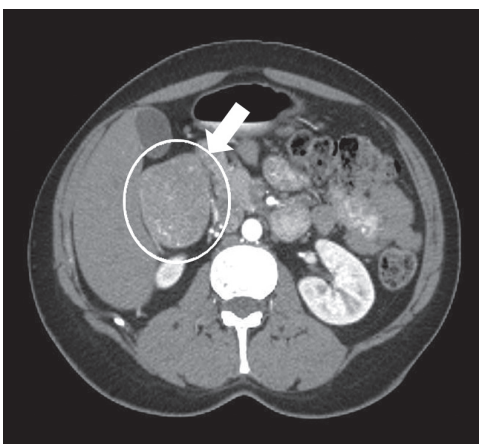

Figure 1. Computed tomography of the tumour of the right adrenal gland. (The tumour outlined with a white line).

Table 1. Plasma hormones before and 2h, 24h and 1-12 months after removal of DHEAS secreting adrenal adenoma

Plasma hormone	Before	After surgical removal or tumor						Normal range
		2h	24h	1 month	3 months	6 months	12 months	
DHEA-S	25.5(hh)	6.6	1.1(ll)	3.61	3.0	NT	*2.3*	mmol/L (1.5-11.5)[1]
Testosterone	20.6(hh)	9.96(h)	1.11	1.55	1.38	NT	*1,19*	nmol/L (0.38-2.7)[2]
Estradiol	519	196	141(l)	266	1088	NT	*626*	pmol/L (183-1769)[3]
Cortisol	260	66(l)	32(l)	201	144	NT	*205*	nmol/L (138-690)
Aldosterone	706(hh)	464(h)	80.5	606(hh)	1189(hh)	1468(hh)	*1058(hh)*	pmol/L (28-444)
Progesterone	16	NT	NT	23	2.9	NT	*NT*	nmol/L (8–78)[4]
17-OH progesterone	4.38(h)	NT	NT	3.0	1.81	1.83	*1.94*	nmol/L (0.33-3.27) [4]
ACTH	1.9	0.6(l)	0.5(l)	3.0	3.7	NT	*5.2*	pmol/L (1.63-14.15)
Renin	4.0	<0.78(l)	<0.78(l)	5.9	9.4	8.7	*2.9*	ng/L (1.6-14.7)
Metanephrine	0.16	0.14	0.01(l)	0.2	0.06	0.12	*0.11*	nmol/L (up to 0.61)
Normetanephrine	0.47	0.46	0.05(l)	0.46	0.17	0.77	*0.22*	nmol/L (up to 1.03)
LH	1.72(l)	NT	NT	2.7	4.87	NT	*4.3*	IU/L (1.9-12) [3]
FSH	2.13(l)	NT	NT	5.0	2.31(l)	NT	*3.1*	IU/L (2.5-10.2) [3]
Prolactin	44.0(l)	NT	NT	50.0(l)	66.2	NT	*170*	mU/L (57-418)

Values in brackets indicate normal ranges. DHEA-S – dehydroepiandrosterone sulfate; ACTH – adrenocorticotropic hormone; LH – luteinizing hormone; FSH – follicle stimulating hormone; NT – not tested; 1 - women aged 35-39; 2 -women; 3 - women, follicular phase; 4 - women, luteal phase; l - low, h – high, hh – very high.

According to the large size of the tumour and high blood level of DHEA-S and testosterone, the tumour was expected to be malignant and surgery was selected as a proper treatment modality.

After laparoscopic removal of 137 g adrenal tumour significant decrease of DHEA-S and testosterone appeared in 2 hours after the surgery and became low in 24 hours.

At the same time estradiol, aldosterone, renin, metanephrine, normethanephrine, 17-OH progesterone, ACTH and cortisol levels were also decreased, then later to the level of adrenal insufficiency. Morphological investigation revealed adrenal adenoma (histology in Fig. 2).

Soon after the surgery, general health improved, but weakness, hot flashes and perspirations appeared. Menses reappeared spontaneously in six weeks and symptoms of menopause ceased.

Seizures did not appear in 12 months after the surgery. Repeated sleep

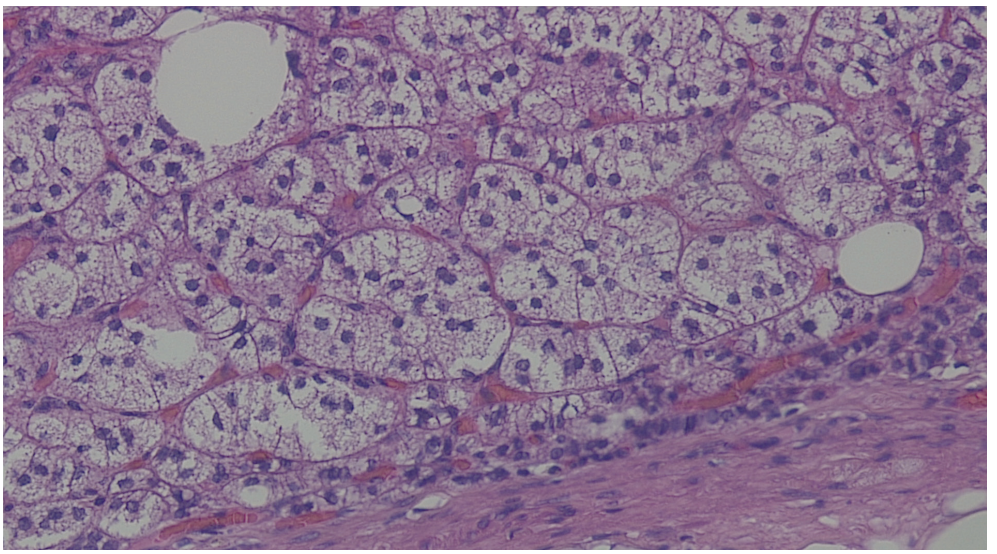

Figure 2. Adrenocortical adenoma. The tumour is incapsulated, composed of small nests or alveolar structures of large vacuolated clear cells with small, monomorphic nuclei. The nuclear/cytoplasmic ratio is low. There is no mitotic activity.

EEG was negative.

Concentration of aldosterone was slightly increased before the surgery and decreased immediately after it, but it was at a barely high level at one, 3 and 12 months after the surgery without signs of primary hyperaldosteronism. Repeated CT of adrenals performed for increasing aldosterone concentration 6 months after surgery did not reveal any change in restant adrenal – no adenoma, no hyperplasia.

Sexual function was evaluated using Female Sexual Function Index (FSFI) (5) and results are shown in Table 2. They indicate that a woman was at sexual dysfunction risk (the FSFI total score ≤ 26. 55) one month before the operation (score - 19.0) and one month after the operation (25.0). The best sexual function was detected 12 months after the operation (score 33.3). Desire, arousal and orgasm were better 6 months after the operation compared to the situation before the manifestation of the disease, 1 month before the operation and 1 month after the operation. Arousal, lubrication, orgasm and satisfaction did not differ at 6 months and 12 months after the operation. Desire score 12 months after the operation was equal to desire score before the manifestation of the disease.

DISCUSSION

Under discussion are 4 interesting new observations found during management of this patient: seizures, menopause symptoms, changes of sexuality and aldosterone.

DHEA-S, testosterone secretion and seizures

Terzolo *et al.* (2) described a clinical picture of 18 women with clinically overt adrenal tumours who under-

Table 2. Female sexual function index (FSFI) in different periods of the disease

FSFI	Before the manifestation of the disease	1 month before the operation	1 month after the operation	6 months after the operation	12 months after the operation
Desire	4.8	3	4.2	6	4.8
Arousal	4.8	2.4	3.9	5.7	5.7
Lubrication	6	3.6	5.7	6	6
Orgasm	4.4	3.6	4.4	6	6
Satisfaction	6	2.8	4.4	5.2	5.2
Pain	1.2	3.6	2.4	1.2	5.6
Total FSFI score	27.2	19	25	30.1	33.3

went surgery. Seven of them had high DHEA-S values, and 4 of these – hirsutism. In this study the sensitivity and specificity of low DHEA-S level in the identification of a benign lesion was 41% and 100% respectively. DHEA-S was elevated in 9 of 11 adrenal neoplasms.

Cases of women with high levels of DHEA-S and testosterone from adrenal tumours are extremely rare. Both of 2 most similar cases were reported as oncocytic adrenocortical carcinoma in a 19-year-old female who presented with acne, hirsutism and irregular menses (6) and 14-year-old girl with hypertrichosis and absence of menarche (7). Another case of 23–year-old female patient with hirsutism, fatigue and fast fatal course of disease was also described (8). In a 58-year–old patient increased DHEA-S (due to adrenal adenoma) was combined with high testosterone, secreted by Sertoli-Leydig cell tumour. Levels of both hormones normalized after an excision of adrenal and ovary tumours (9). No epileptic seizures were noticed in these cases with high endogenic DHEA-S level.

One more incidentaloma in a 54-year-old male patient, proved later to be adrenal oncocytoma with uncertain malignant potential described in this Journal in 2012 (10).

We are presenting the first case where endogenous DHEA-S and testosterone hypersecretion causes epileptic seizures. Disappearance of epileptic seizures after removal of DHEA-S and testosterone secreting tumour enforce this affirmation.

Administration of different doses of exogenous DHEA, which is not recognized as a drug, but food supplement, is widely used for different purposes. Despite postulated pleiotropic effects of DHEA on various tissues and organs, there is a lack of long–lasting prospective trials with DHEA (11). Both Traish (11) and Labrie (12) accentuate no significant adverse or negative effects in men and women, treated with DHEA, but positive effects were inconsistent or absent as well. Adverse events described were mild acne, facial hair growth, ankle swelling, seborrhea and endometrial thickness (11). Traish *et al.* reviewed 90 studies with DHEA treatment in 2639 women with positive, neutral/no or negative findings, but there were no negative findings described.

Treatment of women to improve ovulation possibilities and IVF chances of pregnancy with DHEA is also popu-

lar (13). Usually, adverse or negative side effects are not reported, except one (14). Interestingly, Karp *et al.* describes the onset of late posttraumatic seizure after DHEA treatment in an attempt to improve ovarian oocyte production. This case is regarded as "an anecdotic coincidence" (12).

In our case epileptic seizures appeared due to long-lasting endogenous DHEA-S hypersecretion.

Is this the 2nd anecdotic coincidence?

DHEA-S as proconvulsivant neurosteroid

Early experimental data (15) proved that long– term subcutaneous administration of sulphated neurosteroids pregnenolone sulphate and DHEA-S sulphate produces proconvulsant effects in mice. Intracerebroventricular administration of DHEA-S also induced seizures in a dose-dependent way (16). In a recent review Reddy (17) resumed that sulphated neurosteroids pregnenolone sulphate and DHEA-S are excitatory and produce memory – enhancing and anxiogenic effects and are also proconvulsants and contribute to neurogenesis and neuroprotection.

Resuming available clinical and experimental data about the proconvulsant effect of DHEA-S, it seems likely that only extremely high and longstanding concentrations of endogenous or exogenous DHEA-S in combination with some yet unknown brain changes provoke clinical manifestation of epileptic seizures.

Although menstrual disturbances, weight gain and hyperandrogenism are relatively frequent in women with epilepsy (18), concentration of DHEA-S in women under treatment of epilepsy with antiepileptic drugs is usually lower than in control groups (19, 20). Recent review of epileptic seizures and sex hormones mention also DHEA-S influence in epilepsy (21).

Sudden DHEA-S and testosterone decrease, causing transient menopause symptoms

Transient menopause symptoms: weakness, hot flashes and perspirations are most probably explained by the sudden elimination of testosterone as brain estradiol provider (testosterone – estradiol conversion by aromatase). Spontaneous recovery of menses is a sign of recovery of ovarian function with normal secretion of estradiol by the ovary, after removal of androgenic "blockage" of hypothalamo-hypophyseal axis.

Changes of sexual activity

Clinical case showed that adrenal gland tumour that is producing sex hormones had a negative impact on a woman's sexual function. Our findings in the patient are contradictory to generally accepted hypothesis that androgens have a positive effect on women sexual function (22). We speculate that longstanding excessive stimulation of androgen receptors induces their downregulation and subsequent decrease of sexual function. It takes some months after surgical removal of DHEA-S and testosterone secreting tumour to establish normal testosterone receptor action and sexuality. At twelve months after surgery in-

crease of sexual function is observed at low levels of androgens, a phenomenon similar to androgen receptor upregulation.

It is a well-recognized fact, however, that although hormones may have a modulating effect on female sexuality, there are many other powerful influences, including relationships, psychology, sociology, culture, and past experiences, which at times seem to override the hormonal milieu (23). Probably weight gain, hirsutism and psychological factors played a role on women's sexual pleasure.

In conclusion, we describe clinical, laboratory and sexual behaviour characteristics of a woman with DHEA-S and testosterone secreting tumour and seizures. After unilateral adrenal operation epileptic seizures, amenorrhea, hirsutism, obesity and sexual activity returned to normal and did not appear 12 months of observation after the surgery. The direct causal relation of these symptoms and hypersecretion of DHEA-S and testosterone are strongly suggestive.

Conflict of interest

The authors have no conflicts of interest to declare.

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