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FUNCTIONAL STATUS OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN OPERATED WOMEN WITH CUSHING'S SYNDROME PATIENTS 1,3,6 MONTHS AFTER SURGICAL TREATMENT

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Abstract:

Under observation by the staff of the Department of Neuroendocrinology and Neurosurgery of the RSNPMC of Endocrinology, M3 RUz and RKK for Cushing's Syndrome, 163 patients of fertile age have been registered from 2000 to the present time. Mean age was 27.58±3.4 years (from 17 to 49 years). The average duration of the disease was 4.2 ± 0.2 years. Twenty healthy women of the same age formed a control group. All female patients with SC registered since 2000 (deceased were not included) were distributed by etiology as follows: 1 gr. - patients with ACTH-dependent SC - 130 (79.7%), 2 gr. - with ACTH-independent SC - 30 (18.4%), and group 3 - patients with ACTH-ectopic SC - 3 (1.8%). Before treatment, women with SC in group 1 had a significant increase in basal ACTH, cortisol, prolactin against the background of hyperandrogenemia and ovarian insufficiency ($p<0.05$). In patients with IC in groups 2 and 3, a significant increase in basal values of cortisol, prolactin, and hyperandrogenemia ($p<0.05$) was associated with a non-significant decrease in estradiol and progesterone ($p>0.05$).

In patients with SC with surgical treatment in 1, 2 and groups, normalization of ACTH and cortisol levels was seen 1 month after surgery, but after 6 months the condition remained practically unchanged, $p < 0.05$. One year after surgery we found normal blood hormone levels of ACTH, LH, FSH, cortisol, prolactin in the patients of all three groups.

Keywords: ACTH-dependent Cushing's syndrome, ACTH-independent Cushing's syndrome, pituitary adenoma, prolactin, cortisol, FSH, LH

RELEVANCE:

As early as 1989, Manusharova R.A. was one of the first to present data on the functional state of the GnH system in 119 women with Icenko-Cushing's disease in the active stage, stable clinical remission and after total adrenalectomy. The most pronounced changes in the ratio of pituitary, adrenal and uterine hormones were found in the active stage of the disease, which resulted in NMSC as a hypomenstrual syndrome, polycystic ovarian degeneration and infertility. In stable remission after treatment and after adrenalectomy, hypothalamic-pituitary-adrenal relationships have been found to gradually recover, leading to restoration of the menstrual cycle and fertility [11].

Magiakou M. A. , Mastorakos G, Webste E. in 1997 were among the first to show that the hypothalamic-pituitary-adrenal (HPA) axis and the female reproductive system are interrelated and show a complex relationship, The GnH axis has mainly inhibitory effects on the reproductive axis with corticotropin-releasing hormone (CRH) and CRH-induced propiomelanocortin peptides inhibiting gonadoliberin secretion in the hypothalamus, and with glucocorticoids inhibiting LH secretion as well as estrogen and progesterone. Estrogen-targeted tissues, such as the endometrium, are resistant to the gonadal steroid. These HGH axis effects are responsible for the "hypothalamic" amenorrhoea of stress, depression and eating disorders, as well as for SC-related hypogonadism. Conversely, estrogens directly

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stimulate the CRH gene, contributing to significant hypercorticism and the prevalence of depressive, anxiety and eating disorders in women. Interestingly, some components of the HNH axis and their receptors are present in reproductive tissues, such as ovarian and endometrial CRH, and may be involved in inflammatory processes in the ovary, i.e. ovulation and luteolysis, as well as in implantation and the menstrual cycle. Finally, hypercorticism in the second half of pregnancy can be explained by high placental placental CRH levels. This hypercorticism causes transient adrenal suppression in the postpartum period, which may explain the postpartum depression and autoimmune phenomena of this period (12). Further in 1998 Chrousos G P, Torpy D J, Gold P W. described how the GHN axis has a profound, multi-level inhibitory effect on the female reproductive system. Corticotropin-releasing hormone (CRH) and CRH-induced proopiomelanocortin peptides inhibit hypothalamic gonadotropin-releasing hormone secretion, while glucocorticoids suppress pituitary production of LH and estrogen and progesterone by ovaries and make target tissues resistant to estradiol. Thus, the GHN axis is responsible for 'hypothalamic' stress amenorrhoea, which is also seen in melancholic depression, malnutrition, eating disorders, chronic active alcoholism, chronic excessive physical activity and SC hypogonadism (6).

Sexual disorders due to the development of hypogonadism induced by hypercortisolism are found in 60% of males and 80% of females in most cases. Spermatogenesis is impaired in men, demasculinisation with reduced genital size, decreased libido and potency are detected. In women, generative function and the menstrual cycle are disrupted, up to and including persistent amenorrhoea, primary and secondary infertility (1-5).

Changes in the ovaries in Cushing's syndrome are in most cases involutionary-atrophic and are characterised by moderate sclerosis of the white membrane and cortical layer and a reduction in the number of primordial follicles. In some cases of Icenko-Cushing's disease, sclerotic ovarian degeneration, sometimes with a significant increase in the size of the ovaries, is detected. The latter suggests the possibility of a combination of Itzenko-Cushing's disease and polycystic ovary syndrome, which is to some extent confirmed by the pattern of endometrial changes (6-12). The recovery of menstrual function in women and of potency in men has been observed by several authors (13, 14) to occur in most people in the first 3 months of remission. Repeated sexual dysfunction indicates a relapse of the disease and, in women, a possible pregnancy. A sharp increase in prolactin levels in blood is not a prognostic criterion for the development of ACTH-SC relapse, but may indicate pregnancy [15-18]. Consequently, normalization of sexual function suggests remission of the disease, whereas its recurrence indicates another relapse of ACTH-HSC or ACTH-HSC.

This was the reason for the present study.

The aim of the study was to examine the functional state of the hypothalamic-pituitary-gonadal axis (HGA) in operated women with SC patients 1, 3, 6 months after treatment.

MATERIAL AND METHODS OF RESEARCH:

A total of 308 patients with Cushing's syndrome, including 95 males and 213 females, were followed up in the Department of Neuroendocrinology and Neurosurgery of RSNPMC Endocrinology, M3 RU, for the period from 2000 to present time. Mean age was 27.58 ± 3.4 years (from 17 to 49 years). Duration of disease averaged 4.2±0.2 years. Twenty healthy women of the same age formed a control group. Table 1 shows the number of patients with Cushing's syndrome in the Republic of Uzbekistan by etiological factor among men and women, including those who died. As shown in Table 1, women predominated, which is consistent with the literature..

Table 1.
Number of patients with Cushing's syndrome in the Republic of Uzbekistan by aetiological factor among men and women, including deaths

Forms of Cushing's syndrome	Men	Women	Total
ACTH- WBC	80	168	248
ACTH- HSC	12	40	52
ACTH-ESC	3	4	7
Cyclic Cushing's	0	1	1
Total	95	213	308

Note: ACTH-HSC - ACTH-dependent SC, ACTH-NSC - ACTH-independent SC, ACTH-ESC - ACTH-ectopic SC

Table 2 shows the number of patients of reproductive age (ages 18-35).

Table 2
Number of patients of reproductive age (ages 18-35)

ACTH-HSC	**Reproductive age**			**Non-reproductive age**		
	husband	wife	total	husband	wife	total
ACTH-HSC	57	115	172	11	39	50
ACTH-ESC	7	35	42	2	5	7
Cyclic	3	2	5	0	1	1
Cushing'	0	1	1	0	0	0

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s						
Total	67	153	220	13	45	58

As shown in Table 2, we observed a total of 220 individuals with SC of reproductive age, of whom 153 (69.5%) were women. We then selected these patients and conducted further investigations.

All the patients underwent the following range of investigations, including general clinical, biochemical tests - general blood and urine analyses, blood sugar, lipid spectrum, blood electrolytes (potassium, sodium, chloride, blood calcium), radioimmunological hormonal blood tests (adreno-corticotropic hormone (ACTH), prolactin, cortisol, estradiol, progesterone, free testosterone, small and large dexamethasone tests, cortisol secretion rate) as well as instrumental tests - ECG, X-ray densitometry, ultrasound of the genitals. All patients underwent magnetic resonance imaging (MRI) of the pituitary gland and computed tomography (CT) of the adrenal glands. If necessary, an oral glucose tolerance test was performed.

Methods of ACTH-SC treatment were surgical (TAG and AE, surgical treatment of ACTH ectopic foci), radiation therapy (RT) and drug therapy (MT), and combination therapy (CTe).

All patients with SC were treated in the Department of Neuroendocrinology and Neurosurgery of the RSNPMCE of the Ministry of Health of the Republic of Uzbekistan named after Acad. Y.H. Turakulov. Transnasal adenomectomy of pituitary gland (TAG) was carried out in 93 patients, of them secondary - in 15, in total 108 TAG (Prof. Powell M.P. (London, UK), Dr. Faizullayev R.B., Dr. Makhkamov K.I.). Adrenalectomy was performed in a total of 89 patients as well as in patients with ACTH-HSC (10 observations, Prof. Ismailov S.I.).

The data were processed using Microsoft Excel and STATISTICA_6 (136-140). Significance of differences in quantitative measures (n>12) was determined by Wilcoxon for unlinked ranges, nonparametric Fisher's component randomisation test for independent samples was used to determine significance of small samples (n<12), Fisher's exact test for qualitative values was used. Differences between groups were considered statistically significant at P 0.05.

STUDY RESULTS.

According to the American Association of Endocrinology classification of 2012, all 153 female patients of fertile age with SC registered since 2000 (deceased were not included) were classified according to etiology as follows: 1 gr. - patients with ACTH-dependent SC - 115 (75.2%), 2 gr. - with ACTH-independent SC - 35 (22.9%) and the 3rd group - patients with ACTH-ectopic SC - 2 (1.3%) and the 4th gr. - patients with cyclic Cushing's syndrome -1 (0.6%).

Table 3 shows the functional status of the HGA axis, the levels of ACTH, cortisol and other plasma hormones in the operated patients before surgery and 1, 3, 6 months after treatment. As seen in Table 3, significant increase of basal values of ACTH, cortisol, and prolactin against the background of hyperandrogenemia and ovarian insufficiency ($p < 0.05$) were seen before treatment in women with SC in Group 1. In group 2 SC patients, on the background of significant increase in basal cortisol values (usually 250-720 nmol/l), prolactin (usually up to 5.7 ng/ml), hyperandrogenemia (usually 0.14-6.3 pg/ml), ($p < 0.05$), significant decrease in estradiol and progesterone ($p > 0.05$) was observed. A significant increase in basal values of cortisol, prolactin, and hyperandrogenemia ($p < 0.05$) in patients with SC of groups 3 and 4 was associated with non-significant decrease of estradiol (the norm is 0.34-1.8 nmol/l) and progesterone in plasma (the norm is 11-80 nmol/l), ($p > 0.05$).

Thus, the analysis of hormonal parameters in SC patients at the time of diagnosis of the disease in patients with ACTH-HSC revealed the following: ACTH ranged from 31.8 to 82.4 ng/ml and averaged 57.1 ± 2.99 pg/ml, indicating the clear presence of ACTH-HSC. It should be noted that significant ($p < 0.01$) increase of ACTH level was found in all 115 patients with ACTH-HSC (82.4±4.28), which dictated the need for additional imaging techniques to search for an ectopic focus of ACTH hypersecretion. In contrast, ACTH-HSC patients' ACTH levels remained normal or low, averaging 31.8±0.52 pg/ml.

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Table 3
Functional status of the GGA axis, ACTH, cortisol and other plasma hormone levels in operated women of fertile age before surgery and 1, 3, 6 months after treatment

Groups	Indicators				
		Functional status of the HGA axis	**After 1 month**	**After 3 month**	**After 6 month**
1 group N=115		Before operation	47,9±5,5*	52,6±4,3	42,2±3,7*
	ACTH 82.4±4.3*		436,7±21,3*	723,4±18,3*	545,6±18,7*
	Cortisol, 934.4±8.3*		0,34±0,06 *	0,44±0,04	1,4±0,03
	Estradiol 0.14±0.02 *		8,8±0,02 *	12,5±0,03	31,9±0,04
	Progesterone 1.5±0.03 *		4,6 ±0,3	3,8 ±0,3	3,6 ±0,4
	Prolactin 17.6±0.5 *		4,2±0,3*	2,1±0,3*	0,2±0,04
2 group N=35	Free T 6.3 ±0.2 *		43,4±4,3 *	46,1±3,2 *	47,9±4,6*
	ACTH 51.8 ±0.5		439,8±19,9*	327,6±16,3*	322,1±17,3*
	Cortisol 846,5±14,6*		0,37±0,06	0,35±0,04	1,1±0,03
	Estradiol 0,11±0,02*		10,6±0,3	13,9±0,7	27,6±0,6
	Progesterone 6,4±0,2*		4,8 ±0,6	3,4 ±0,6	3,2 ±0,3
	Prolactin 14,8±0,8		2,2±0,6*	0,8±0,04*	0,2±0,05
3 group N=2	Free T 7.3 ±0.3*		28,4±2,5	25,4±3,3 *	23,4±3,4 *
	ACTH 38.3 ±2.9		335,6±13,7*	327,5±14,2*	323,4±16,4*
	Cortisol 898.9±18.3*		0,55±0,07	1,1±0,03	1,3±0,02
	Estradiol 0.17±0.04*		17,2±0,8	23,6±0,7	27,6±0,3
	Progesterone 2,4±0,03*		7,8 ±0,7	3,5 ±0,7	3,4 ±0,3
	Prolactin 21.3±0.6		3,3±0,2*	1,7±0,4*	0,1±0,02
4 group N=1	Free T 5.3 ±0.6*		44,4±2,7	35,7±2,3	39,6±2,6
	ACTH 45.3 ±3.1		345,9±12,8*	387,8±13,9*	361,2±14,5*
	Cortisol 898,9±18,3*		0,47±0,03	1,1±0,08	1,3±0,04
	Estradiol 0,15±0,06*		12,8±0,8	22,6±0,2	33,2±0,8
	Progesterone 1.7±0.04*		4,9 ±0,2	3,3 ±0,3	3,4 ±0,2
	Prolactin 16.8±0.6		3,8±0,7*	1,4±0,2*	0,1±0,04
	Free T 5,7±0,4*			21,4 ±0,3	
	ACTH pg/ml - up to 50 pg/ml			272,2 ± 2,3	

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	Cortisol- 250 to 720 nmol/l in the morning		1,3 ±0,3
	Estradiol, nmol/l		24,5 ±3,2
	Progesterone, nmol/l		4,2 ±0,4
	Prolactin, ng/ml		0,3±0,02

*Note: * significant difference in comparison to pre-treatment data, where * is P < 0.05 difference to control, in dynamics, SvT - free testosterone*

According to international standards, we investigated the rhythm of blood cortisol (K) and urinary cortisol daily secretion (UCR). In patients with ACTH - WBC, despite significantly elevated levels of K, the rhythm of its secretion during the day was maintained, tending to decrease in the evening. Patients with adrenal or ectopic hypercorticism had an impaired rhythm with significantly higher ($p<0.01$) K values at 18:00 - 1185±67.8 nmol/l and 1132±54.8 nmol/l and at 23:00 - 970.7±27.3 and 1482±46.9 nmol/l respectively, compared to pituitary SC.

Against the background of BPPD, blood cortisol levels were suppressed by 61.3% in patients with ACTH-MSH, by 39.2 and ACTH-ESH by 33.3%, i.e. there was no sufficient suppression of cortisol levels in the last 2 groups, which indicates the presence of an autonomous focus of cortisol or ACTH hypersecretion, which we searched for in our subsequent work phases.

Thus, we established hyperandrogenism and hypercortisolemia in all patients before treatment.

Further, we studied the functional state of the HGA axis, ACTH and plasma cortisol levels in the operated patients 1, 3, 6 months after treatment.

In surgically treated SC patients in Group 1 a month after surgery normalization of plasma ACTH, cortisol, prolactin, estradiol, progesterone and free testosterone levels was observed, and 6 months later this condition persisted, $p < 0.05$.

In female patients with IC with surgical treatment in Group 2, the levels of ACTH, cortisol, prolactin, estradiol, progesterone and free testosterone in plasma were normalized 1 month after surgery, but after 6 months the condition remained practically unchanged, $p <0.05$.

In patients with SC with surgical treatment in groups 3 and 4 the levels of ACTH, cortisol, prolactin, estradiol, progesterone and free testosterone in plasma were normalized 1 month after surgery and the condition was the same after 6 months, $p <0.05$.

After 6 months all the surgically treated SC patients in the 4 groups developed compensatory state against the background of ZGT (they were treated with prednisolone at a dose of 5 to 15 mg). One year after surgery, we found normal blood hormone levels of LH, FSH, ACTH, cortisol and prolactin in all three groups. One year after surgery, only 1 patient in group 1 (2.1)% was able to become pregnant. One year after transnasal pituitaryectomy, 30 women out of 128 (23.07%) with ACTH-HSC achieved pregnancy without stimulation therapy. Only 2 patients (25%) in Group 3 also became pregnant. The main aim of treatment of patients with SC is to achieve remission. As remission promotes a reduction in total body fat mass, it improves cardiovascular FR. It has been proved that K level in the early postoperative period can be a prognostic criterion of SC recurrence in the nearest and distant periods.Table 4 shows the hypercorticism process activity in different forms of the disease in women.

Table 4

Characteristics of patients of fertile age with SC according to the registry (n=153)

Forms of Cushing's syndrome	active remission	stage	total
ACTH-HSC	42	73	115
ACTH-HSC	5	30	35
ACTH-ESC	1	1	2
Cyclic Cushing's syndrome	0	1	1
Total	48	105	153

It was found that remission was achieved in 73 (63.4%) women with ACTH-HSC, and remission was not achieved in 42 (36.6%) patients overall. A high remission rate was found in ACTH-HSC patients, which amounted to 30 (85.7%) cases, and only in 2 cases the disease relapsed due to an unfavorable outcome with the development of metastases after surgery for adrenal carcinoma.

According to the findings of Narimova G.D. , in 2018, remission was achieved in 71% of patients with

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SC by RUz. Moreover, the lowest remission was observed in patients with ACTH-HSC and amounted to 65.3%, which is similar to the data in the literature.

To summarize our study, it should be emphasized that in the postoperative period remission was achieved in 73 (63.4%) of 115 patients with ACTH-HSC, in 16.7% of them relapse occurred, and in 42 (36.5%) remission was not achieved. Of the 35 women with ACTH-NSC, 30 (85.7%) achieved remission after AE and 5 (14.3%) did not achieve remission.

DISCUSSION OF RESULTS.

It is known that the treatment goals for a patient with SC are remission of hypercorticism, adequate treatment of comorbidities, restoration of the hypothalamic-pituitary-adrenal axis, preservation of fertility and pituitary function, and improvement of visual disturbances in cases of macroadenomas with suprasellar growth. Transphenoidal pituitary surgery is the main treatment option in most cases, even in macroadenomas with a low probability of remission. In cases of surgical failure, other subsequent pituitary surgery may be indicated in cases with persistent tumour on post-surgical magnetic resonance imaging (MRI) and/or analysis of adrenocorticotropic hormone-positive (ACTH+) pathology of a positive pituitary adenoma in the first procedure. Medical treatment, radiation therapy and adrenalectomy are other options when transsphenoidal pituitary surgery fails. There are several treatment options, although cabergoline and ketoconazole are most often used alone or in combination. Different therapeutic approaches are often needed on an individual basis, both before and especially after surgery, and these must be individualised.

CONCLUSIONS.

1) Prior to treatment, significant increases in basal ACTH, cortisol, prolactin values on the background of hyperandrogenemia and ovarian insufficiency ($p < 0.05$) were observed in women with SC in Group 1. In group 2 and 3 SC patients, a significant increase in basal values of cortisol, prolactin, and hyperandrogenemia ($p < 0.05$) was accompanied by a not significant decrease in estradiol and progesterone ($p > 0.05$).

2) In women with SC with surgical treatment in 1, 2 and groups, normalisation of ACTH and cortisol levels was seen 1 month after surgery, while levels remained practically unchanged after 6 months, $p < 0.05$.

3) One year after surgery we found normal blood hormone levels of ACTH, LH, FSH, cortisol, prolactin in patients of all three groups.

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