Tretyak O. Clinical and laboratory characteristics of patients with adrenal incidentalomas in the differential diagnosis of subclinical hypercortisolism. Journal of Education, Health and Sport. 2020;10(11):238-244. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.11.023
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.11.023
https://zenodo.org/record/4416023

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 16.10.2020. Revised: 30.10.2020. Accepted: 30.11.2020.

Clinical and laboratory characteristics of patients with adrenal incidentalomas in the differential diagnosis of subclinical hypercortisolism

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Abstract

Clinical and laboratory characteristics of patients with adrenal incidentalomas in the differential diagnosis of subclinical hypercortisolism. O. E. Tretyak.

Purpose. Determination of the prevalence of subclinical Cushing's syndrome among patients with adrenal incidentalomas; determination of the diagnostic consideration of clinical and laboratory parameters used for the diagnosis of endogenous subclinical hypercortisolism.

Methods. Retrospective analysis of data from 310 patients, who underwent a surgery for unilateral/bilateral adrenal masses. A comparative analysis of the two groups was carried out; the groups were divided based on the results of postoperative pathohistological study. Group 1 included 244 patients with hormonally active masses - adenomas (210), PBMAH (31), PPNAD (3); Group 2 included 66 patients with inactive masses. There were assessed the prevalence of hypertension, DM 2, overweight and the results of laboratory studies of the cortisol level after dexamethasone suppressive test, ACTH, and daily urine-free cortisol excretion.

Results. Patients with hormonally active masses are older (mean age is 52.7 years); 68.4% of patients in group 1 haveAH, 27% haveDM2 (group 2, respectively, 36.4% and

13.6%). There are no differences between groups as to the presence of overweight and obesity. 22.5% of patients of group 1 were confirmed to havePA, in most cases against the background of bilateral masses. The parameter of cortisol after DST has the best diagnostic consideration – sensitivity 90.2%, specificity 74% at a cut-off point level of 1.7 μcg/dL; for ACTH <10 pg/mL, the sensitivity is 71.4% and the specificity is 92.6%. Daily cortisol urine-free excretion has the third most significant diagnostic consideration (sensitivity 71.4%, specificity 81.8%, COP 238 mg/24 h.), which limits the application of this parameter for the confirmation of high levels of cortisol in patients with incidentalomas. Cases of bilateral adrenal hyperplasia should be considered as a probable variant of PBMAH syndrome, requiring further laboratory testing for PA.

Key words: **adrenal incidentaloma; subclinical hypercortisolism; subclinical Cushing's syndrome; autonomic cortisol secretion; primary hyperaldosteronism.**

Today the issue of diagnosis and treatment of patients with subclinical hypercortisolism against the background of adrenal massesis of topical interest. According to the retrospective studies data, patients with subclinical hypercortisolism have an increased risk of cardiovascular diseases and mortality from all causes [1, 2]. The tactics of supervision and the validity of surgical treatment of subclinical Cushing's syndrome (CS) are the subject to further discussion [3]. Existing randomized studies are insufficient to explain the long-term effects of surgical treatment, confirming the relationbetween metabolic disorders and high cortisol levels [4]. Existing recommendations for the examinations of patients with adrenal incidentalomas [5] determine laboratory criteria for the presence of autonomous cortisol secretion, however, the validity of the surgeryshall be decided on by the physician based on a set of data including the patient's age, metabolic disorders, the degree of hypercortisolism, densitometric characteristics of the adrenal mass [6, 7]. The article presents a retrospective analysis of the results of the examination of patients who underwent a surgery for unilateral/bilateral adrenal masses at the Ukrainian Scientific and Practical Center for Endocrine Surgery for the period from 2009 to 2015. When processing data of 503 patients, patients with a confirmed pheochromocytoma, including those within the MEN 2 syndrome (68 patients) were excluded from the study; patients with a confirmed adrenocortical cancer (11 patients) and secondary adrenal lesions that metastatic from tumors of other localizations (9 patients); 64 patients with isolated primary hyperaldosteronism (PA); patients with clinical CS against the background of corticosteroma (31 patients) and ectopic adrenocorticotropic hormone (ACTH) syndrome (4 patients). The data of 310 patients, which were divided into

two groups for comparative analysis, were analyzed. They were divided according to the data of postoperative pathohistological study (PHS): adrenal adenomas/hyperplasias (Group 1; 244 patients; 78.7% of all patients, who underwent a surgery) and hormonally inactive masses (Group 2; 66 patients; 21.3%). Characteristics for comparative analysis included objective data (age, sex); clinically assessed presence of metabolic syndrome components – overweight, arterial hypertension (AH), type 2 diabetes mellitus (DM2). Confirmation of endogenous hypercortisolism included the level of cortisol after dexamethasone suppressive test (DST), ACTH plasma, daily urine-free excretion cortisol (UFC). In group 1, 210 (67.7%) patients were confirmed to have adenomas with autonomous cortisol secretion, including in combination with hyperaldosteronism. PAwas diagnosed in 55 patients (22.5% of all hormonally active masses). 31 patients (12.7%) with bilateral adrenal masses were confirmed to have PBMAH syndrome (Primary bilateral macronodular adrenal hyperplasia); according to the PHS, 3 patients with bilateral masses (1% of all hormonally active masses), were confirmed to have PPAND (Primary pigmented adrenalnodular disease syndrome). Group 2 included 66 patients (21.3% of those, who underwent a surgery) with hormonally inactive masses(myelolipomas – 18 cases, cysts – 34, ganglioneuromas – 3, myxome – 2, hematomas – 9). Statistical processing included Shapiro-Wilk test for normality. For indicators with normal distribution, the mean ± standard error of the mean (M ± SE) was used. For indicators that did not correspond to the normal distribution, the median was used (Me, Q25; Q75 percentile). The significance of the differences between the groups was assessed using the Student's t-test and the Mann-Whitney U test. When comparing the parts, the angular Fisher transform was used. In group 1, when comparing patients with adenomas and bilateral masses (PBMAH, PPNAD syndromes), there was no significant difference in age and BMI; women predominate in all groups. AH is found in 64.3% of patients with adenomas, 90.3% of patients with PBMAH, and 100% of patients with PPNAD syndrome. It is quite probable that the cause is a combination of high levels of cortisol and aldosterone against the background of macronodular hyperplasia – 48.5% of patients with PBMAH were confirmed to havePA; in PPNAD cases, this is associated with the degree of cortisolemia [8]. The proportion of patients with DM2 is practically the same in all subgroups ≈ 30% (Tab. 1).

BMI, bodymassindex; AH, arterial hypertension;DM2, diabetes mellitus 2 type; PA, primeryaldosteronism; significantresults ($p< 0,05$) areinbold.

Comparison of patients in groups 1 and 2 demonstrates the same prevalence of women, however, group 2 includes more men – 37.9% versus 20.5%. Patients in group 1 are significantly older (Tab. 2).

Table 1. Demographic and clinical characteristics of 244 patients (Group 1)

	Adenomas (n=210)M ± SE	PBMAH (n=31)M ± SE	PPNAD(n=3)
Age, years old	53,8 ±12,7	55 ± 7,8	43(29-53)
BMI, kg/m^2	30,4±5,2	29,9±5,2	29,3
Sex(m., %)	37/17,6	9/29,03	2/66,7
AH, n/%	135/64,3	28/90,3	3/100
PA, n/%	28/13,3	15/48,4	-
DM2, n /%	56/26,7	8/25,8	1/33,3

Table 2. Demographic, anamnestic and clinical parameters of patients, who underwent a surgery forincidentaloma adrenal

	Group 1 (n=244) M ± SE Me (Q_{25}; Q_{75})	Group 2 (n=66) M ± SE Me (Q_{25}; Q_{75})	p
Age, years old	**52,7 ± 0,8**	**46,0 ± 1,7**	**<0,001**
BMI, kg/m^2	29,2 ± 0,3	29,3 ± 1,1.	>0,05
Sex (m., %)	**50/20,5**	**25/37,9**	**<0,01**
Overweight BMI, kg/m^2 ≥25, n /% - BMI 25-29, n /% - BMI ≥30, n /%	196 /78,7 ± 2,6 89/36,5 107/43,9	43 /69,7 ± 5,7 23/9,4 20/40,9	>0,05
Present of AH, n/%	**167/68,4 ± 3,0**	**24/36,4± 5,9**	**<0,01**
Present of PA, n/%	55/22,5 ± 2,7	-	-
Present of DM2, n /%	**56/27,0± 2,8 %**	**9/13,6± 4,2**	**<0,01**
Bilateral masses, n/%	34/13,9	-	-

BMI, body mass index; AH, arterial hypertension;DM2, diabetes mellitus 2 type; PA, primery aldosteronism; significant results (p< 0,05) are in bold.

There is no significant difference in BMI was reported. 78.7% of patients in group 1 and 69.7% in group 2 were overweight; of them, 43.9% of the total number of patients in group 1 had obesity (BMI ≥30), among patients in group 2 – 40.9%. Thus, there were no difference between the groups of patients with hypercortisolism and hormonal imbalance in the presence of one of the main components of the metabolic syndrome – overweight. A significantly greater number of patients with hormonally active masses has AH (68.4% in group 1, 36.4% in group 2). It should be noted that 36 patients were confirmed to have concomitant hyperaldosteronism (22.5% of the total number of patients in group 1). Thus, most patients with hormonally active masses have AH, however, in a quarter of cases it is caused by a combination ofhigh levels of cortisol and aldosterone, as confirmed by the data of other studies [9, 10]. DM 2 is found in 27% of patients in group 1 versus 13.6% in group 2. The prevalence of DM 2 in patients with hormonally active masses is significantly higher, as

confirmed by the results of other authors [11]. Comparative analysis of laboratory parameters for the diagnosis of hypercortisolism demonstrates significant differences between the groups (Table 3).

Table 3. Comparative analysis of the results of laboratory tests for the diagnosis of endogenous hypercortisolism

	Group 1 (n=244) Me (Q_1; Q_3)	Group 2 (n=66) Me (Q_1; Q_3)	p
ACTH, pg/mL	**8,1(5,0; 14,0)**	**19,0(14,8; 22,05)**	**<0,001**
UFC, µg/24 h.	**302(220,5; 469,0)**	**205(172,0; 233,0)**	**<0,001**
Cortisol DST, µcg/dL	**3,25(2,3; 5,43)**	**1,25(0,8; 1,85)**	**<0,001**

ACTH – adrenocorticotropic hormone; UFC, urine-free cortisol; cortisol DST, cortisol level after an overnight 1-mg dexamethasone suppression test; significant results (p< 0,05) are in bold.

The average value of the main screening test – the cortisol DST in group 1 is significantly higher – 3.25 µcg/dL versus 1.25 µcg/dL in group 2. The median ofUFCin group 1 is 302 µg/24 h, 205 µg/24 h in group 2. It should be noted that both theseparameters are within the reference range (the norm is determined by the chemiluminescence immunoassay method 58–403 µg/24 h) ACTH plasma level in group 1is significantly lower – 8.1 pg/mL versus 19 pg/mL in group 2. To determine the diagnostic consideration of laboratory parameters, an ROC analysis (Receiver Operating Characteristic) was carried out. The quality of the parameters was assessed according to the area under the curve (AUC). For DST, the AUC parameter was 0.883 (Fig. 1), ACTH – 0.815, daily cortisol excretion 0.803– parameters in the range of 0.8–0.9, which corresponds to the 'very good' assessment of the quality of the model.

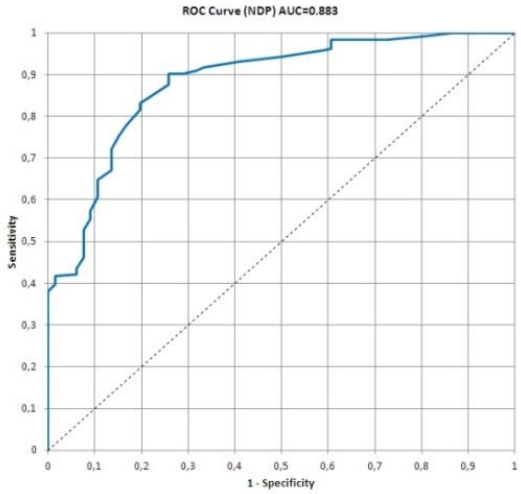

Fig.2. AUC for DST cortisol

The parameter of cortisol DST has the highest diagnostic consideration - sensitivity (Se) 90.2%, specificity (Sp) 74% at a cut-off point (COP) level of 1.7 μcg/dL, which is lower than that recommended by clinical guidelines [5]. Having analyzed the data, it has been found that in patients with adrenal incidentalomas, the ACTH level of ≤ 10 has the maximum specificity (92.6%) for the confirmation of endogenous hypercortisolism (Tab. 5).

Table 5. Characteristics of the diagnostic strength of laboratory finding in the diagnosis of endogenous hypercortisolism in patients with adrenal masses

	COP	Se,%	Sp,%	AUC	Youden index J
Cortisol DST, μg/dL	1,7	90,2	74,2	0,883	0,644
ACTH, pg/mL	10	63,1	92,6	0,815	0,557
UFC, μg/24 h.	238	71,4	81,8	0,803	0,532

ACTH, adrenocorticotropic hormone; UFC, urine-free cortisol; cortisol DST, cortisol level after an overnight 1-mg dexamethasone suppression test;

The parameter of daily cortisol excretion has the third most significant diagnostic consideration for the confirmation of subclinical hypercortisolism when examining patients with incidentalomas – sensitivity 71.4%, specificity 81.8%, with COP below the upper reference limit – 238 mg/24 hours.

As a matter of record, it could be argued that symptom – free hypercortisolism without specific clinical signs can be confirmed in 48% of patients with adrenal incidentalomas. Most patients with subclinical hypercortisolism have the following clinical signs, in particular, arterial hypertension and type 2 diabetes mellitus. The most informative diagnostic test is cortisol after the overnight 1-mg dexamethasone suppression test. ACTH plasma level is the second most important laboratory sign of subclinical CS with a rational application of a cut-off point of ≤ 10 pg/mL. Parameters of daily urine-free cortisol excretion in most of the patients with subclinical hypercortisolism are within the reference range, which limits the application of this parameter for screening patients with incidentalomas. Bilateral adrenal hyperplasia should be considered as a probable variant of PBMAH syndrome, however, there might be a combined excess cortisol secretion and aldosterone, requiring laboratory testing for PA.

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