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Hormonal and metabolic evaluation of adrenal incidentalomas

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The biochemical and hormonal data in patients with adrenal incidentalomas were evaluated to compare the differences between adrenal adenomas and other benign lesions and to find the relationship between metabolic parameters and adrenal hormones. Ninety two patients (29men, age 20-90 years) with incidentally discovered unilateral or bilateral adrenal masses detected on CT were included in this study for the reasons others than adrenal pathology. Glycemia, cholesterolemia, triglyceridemia, hormonal evaluation including plasma ACTH, plasma aldosterone, plasma renin acitivity, overnight dexametasone test, ACTH test, free plasma metanephrines, urinary catecholamines were determined. In the group of patients with adrenal masses the prevalence of arterial hypertension was three fold higher, the prevalence of DM was approximately five fold higher and the prevalence of the overweight and obesity two fold higher than is reported in the general population. The most frequent adrenal masses were nonfunctional masses, the occurence of functional lesions was as follows: steroid enzymopathies (an exaggerated response of 17-OHP indicating a possible 21-hydroxylase deficiency), subclinical Cushing syndrome, primary aldosteronism and pheochromocytoma (5%, 2%, 2% and 1% respectively). There were no significant differences in evaluated data between patients with adenomas and hyperplasia and also no significant difference in evaluated data between lesions smaller than 3 cm and lesions greater than 3 cm. We did not find any correlations between plasma cortisol and lipid values. In this study we confirmed a higher prevalence of symptoms characteristic for different metabolic syndromes in these patients with adrenal incidentalomas, which indicate systematic screening for the metabolic syndrome including evaluation of the insuline resistance in this patients.

Key words: adrenal incidentaloma, cholesterol, triacyglyceroles, obesity, hypertension, steroid enzymopathy

Adrenal incidentalomas are unsuspected, clinically silent adrenal lesions discovered incidentally by imaging techniques done for reasons unrelated to the adrenal glands. Due to the high resolution of ultrasonography, CT and MRI, as well as the greater number of radiological investigations, identification of adrenal incidentalomas has increased. Their prevalence on CT series ranges for 0,5 up to 4,4% of patients [1, 2]. In some series these tumors represent more than 50% of all adrenal diseases. Therefore the management of adrenal tumors is becoming an increasingly important aspect of health care [3, 4].

Unfortunately we still do not have an exact criteria for diagnosis and therapy of nonfunctional adrenal masses as well as for the diagnosis and treatment of subclinical Cushing´s syndrome [5, 6]. Despite the fact that adrenal adenomas are frequently associated with the metabolic syndrome, an exact explanation for such relationship is not known. Moreover the relations between biochemical and hormonal parameters in cohorts of patients with adrenal masses are uncertain.

Aim of this study was to evaluate biochemical as well as hormonal data in patients with adrenal incidentalomas, to compare the differences between adrenal adenomas and other benign lesions and secondly to find the relationship between metabolic parameters and adrenal hormones.

Patients and methods.

Group of patients consisted of ninety two subjects with incidentally discovered unilateral or bilateral adrenal masses detected on CT that was performed for the reasons others than adrenal pathology.

Average age of patients was 56 years (range 20- 90 years, median 55 years). All group comprised 29 men and 63 women (32% v. s. 68%). The size of masses ranged from 8 up to 120 mm.

There were evaluated following data: At first concomitant occurrence of the symptoms of the metabolic syndrome was

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determined, i.e. we evaluated patients for the presence of arterial hypertension, overweight or obesity, diabetes mellitus as well as disturbances of the lipid metabolism.

The presence of above mentioned symptoms was searched using history, physical examination and laboratory methods with the measurement of fasting and postprandial glycaemia, cholesterolemia and triglyceridemia. Overweight and obesity were tested using calculated body mass index (BMI = weight/height ^{2})

Secondly hormonal and biochemical evaluations to detect of endocrine overproduction or steroid enzymopathy were performed.

1. Hypercortisolism. A. *Overnight Dexametason test*: blood sample for the measurement of plasma cortisol was taken on the morning at 7 o´ clock, at 11 o´clock p.m. at the same day a 1mg of dexametasone was administered orally and a blood sample for the evaluation of plasma cortisol was collected on the following day. A decrease of plasma cortisol under 50% of the baseline value indicated a normal response and ruled out the Cushing syndrome.

B. *Circadian rhythm of plasma cortisol.* A midnight decrease of plasma cortisol more than 50% of morning value was postulated to be a normal.

C. *Plasma adrenocorticotrophic hormone (ACTH).* Blood sample for the evaluation of plasma ACTH was taken on the morning at 7 o´clock.

D. *Detection of the subclinical Cushing syndrome.* Diagnostic criteria of National Italian Group on Adrenal Tumors were used for the detection of subclinical Cushing syndrome (7).

- lack of clinical symptoms of glucocorticoid overproduction,
- the presence of minimally two abnormities in the hypotalamic- pituitary-adrenal axis, i.e. lack of supression of plasma cortisol in overnight Dexametason test, supressed plasma ACTH or dehydroepiandrosterone sulphate (DHEAS) and lack of supression of the midnight plasma cortisol.

2. Primary aldosteronism. A. *Presence of hypokalemia*. The serum potassium level 3,8 mmol/l was considered to be a cut off value for the definition of hypokalemia.

B. *Aldosterone/renin ratio (ARR)* was calculated from the morning casual plasma values of aldosterone (PA) and plasma renin activity (PRA). ARR 400 and more indicated a further tests confirming the diagnosis of primary aldosteronism.

3. Catecholamines overproduction. A free plasma metanephrines as well as urinary catecholamines – adrenaline and noradrenaline were measured for the detection of pheochromocytoma.

4. Steroid enzymopathy. In this study we performed tests for the detection of two most frequent steroid enzymopathies, i.e. late onset deficiency of 21-hydroxylase and the deficiency of 3-beta-hydroxysteroiddehydrogenase (3-beta-HSD).

ACTH test was performed for the detection of steroid enzymopathies. Blood sample for the evaluation of 17- hydroxyprogesterone (17-OHP) and dehydroepiandrosterone (DHEA) was taken on the morning at 7 o´ clock. After blood sampling a synthetic analogue of ACTH – tetracosactide hexaacetate (Synacthen, Novartis, Switzerland) was administered intravenously in the dosage of 0.25 mg. Blood samples were collected after 30 and 60 minutes. An increment of 17-OHP of 12 mmol/l (8) or its plasma value higher than 30nmol/l (9) after ACTH administration indicated a 21- hydroxylase deficiency and an increase of DHEA above 20 ng/ml indicated a diagnosis of 3- beta HSD deficiency (10).

Plasma ACTH, PRA, PA, 17 OHP as well as DHEA were measured radioimmunoanalytically using kits Immunotech (France).

Urinary catecholamines were evaluated using high resolution fluid chromatography, cholesterol, triacylglyceroles, glycemia and serum potassium were measured routineously.

Statistical analysis. Mean values of evaluated data are presented as mean + SEM. The differences between groups were tested using unpaired T test and the relationship between parameters was determined using linear regression analysis and associative method in the statistical programm SAS.

Results.

The prevalence of symptoms of the metabolic syndrome in the group of patients in comparison with the prevalence in general population is shown in Table 1.

In the group of patients with adrenal masses the prevalence of arterial hypertension was three fold higher than the reported in general population, the prevalence of DM was approximately five fold higher and the prevalence of the overweight and obesity two fold higher than is reported in the general population. Moreover, the disturbances of lipid metabolism were detected in the two fold higher prevalence than reported in the Slovak population.

The presence of adrenal endocrinopathies in the group of patients with adrenal masses is shown on Graph 1. The most frequent adrenal masses were nonfunctional masses,

Table 1 The prevalence of symptoms of the metabolic syndrome in the group of patients in comparison with the prevalence in general population.

Prevalence	N	%	Prevalence in the Slovak population
Hypertension	51	55	15-20 [15]
Diabetes mellitus 2 type	20	22	4-8 [16]
Hyperlipidemia	56	61	30[17]
Overweight, obesity	47	51	25-30[18]

the occurence of functional lesions was as follows: steroid enzymopathies (an exaggerated response of 17-OHP indicating a possible 21-hydroxylase deficiency), subclinical Cushing syndrome, primary aldosteronism and pheochromocytoma (5%, 2%, 2% and 1% respectively).

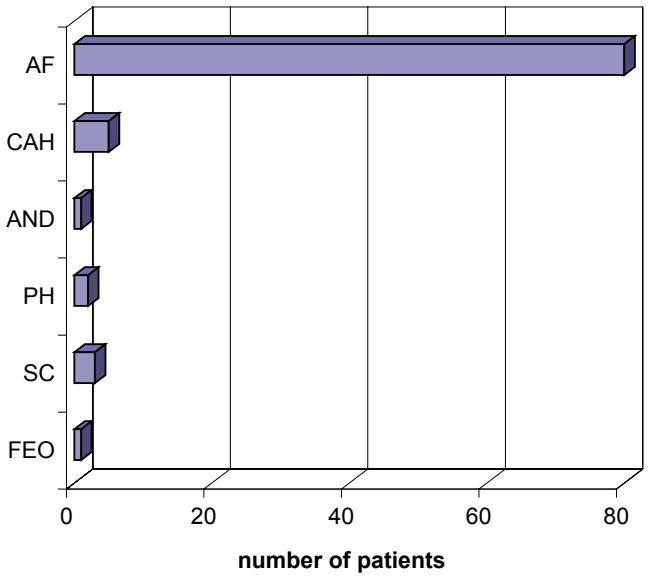
Group of patients was divided into two groups according to CT characteristics of the adrenal mass. First group consisted of patients with the typical CT characteristics of adenoma and the second one consisted of patients with the other lesions which included adrenal carcinoma (2), MTS (6), pheochromocytoma(1), bilateral or unilateral hyperplasia (18), cyst (6), pseudoadrenal structure (2), malignant lymphoma (2), myelolipoma (5), lipoma (2), haemangioma (1), ganglioneuroma (2), actinomycosis(1).

Mean values of the measured parameters in both groups of patients are shown in Table2.

There were no significant differences in evaluated data between patients with adenomas and hyperplasia.

There were no significant differences in measured data in patients with adrenal masses under 3 cm of size in comparison with adrenal masses with the size 3 cm and more. Results are shown in Table 3

We did not find any correlations between plasma cortisol and lipid values.



Graph 1 The presence of adrenal endocrinopathies in the group of patients with adrenal masses.

(FEO = feochromocytoma, SC = subclinical Cushing syndrome, PH = primary hyperaldosteronism, AND = androgen overproduction, CAH = late onset steroid enzymopathy, AF = nonfunctional adrenal masses)

Table 2 Mean values of the measured parameters in all group, adenomas and other lesions.

Parameter	All group (n= 92)	Adenomas (n = 44)	Other lesions (n = 48)	significance
S-K (mmol/l)	4.1 + 0.06	4.1 + 0.1	4.1 + 0.08	NS
Cholesterol (mmol/l)	5.1 + 0.21	5.2 + 0.4	4.9 + 0.22	NS
Triacylglyceroles (mmol/l)	2.2 + 0.16	1.99 + 0.23	1.86 + 0.23	NS
U-adrenalin (nmol/l)	29.3 + 9	38.3 + 20	24.2 + 11	NS
U-noradrenalin (nmol/l)	345.7 + 43	381 + 75	343 + 55	NS
ACTH (pg/ml)	15.6 + 2.0	17 + 4	15 + 1.6	NS
Plasma cortisol (umol/l)	0.39 + 0.01	0.38 + 0.03	0.4 + 0.002	NS
Plasma cortisol arter DXM (umol/l)	0.07 + 0.008	0.06 + 0,01	0.08 + 0.01	NS
PRA (ng/ml/h)	1.8 + 0.3	2.1 + 0.53	1.52 + 0.3	NS
PA (pg/ml)	107 + 13	128 + 21	86 + 14	NS

Table 3 Hormonal and biochemical data in patients with adrenal masses according to size of the mass.

Parameter	Size < 3 cm (n = 47)	Size > 3 cm (n = 45)	significance
S-potassium (mmol/l)	4 + 0.06	4.1 + 0.11	NS
Cholesterol (mmol/l)	5.3 + 0.3	4.9 + 0.3	NS
Triacylglyceroles (mmol/l)	2.2 + 0.17	2.2 + 0.4	NS
U-adrenalin (nmol/l)	35 + 16	25.4 + 12	NS
U-noradrenalin (nmol/l)	357 + 63	338 + 60	NS
ACTH (pg/ml)	13.9 + l.9	18.7 + 4.4	NS
Plasma coritosol (umol/l)	0.42 + 0.02	0.37 + 0.02	NS
Plasma cortisol after DXM (umol/l)	0.06 + 0.01	0.07 + 0.01	NS
PRA (ng/ml/h)	2.02 + 0.5	1.6 + 0.3	NS
PA (pg/ml)	116 + 19	98.8 + 17	NS

Discussion.

Incidentally discovered adrenal masses are mostly benign, asymptomatic lesions, often arbitrarily considered as nonfunctioning tumors. In agreement with previous studies in our group of patients with adrenal masses there was found a higher prevalence in women than in men. Masses were more commonly unilateral than bilateral.

Although the management of adrenal masses is still controversial and we do not have the exact informations about the prevalence of subclinical hypercortisolism, recent studies confirmed a high prevalence of the symptoms of the metabolic syndrome in patients with adrenal incidentalomas particularly adrenal adenomas [11, 12, 13, 14] . Italian multicentric study on 1004 patients with adrenal incidentalomas found arterial hypertension in 41%, diabetes mellitus 10% and obesity in 28% patients, respectively [7)] Similarly in our study the prevalence of arterial hypertension, diabetes mellitus type 2, obesity as well as hyperlipidemia was higher than reported in Slovak general population [15, 16, 17, 18].

This higher prevalence of the metabolic syndrome establishes the question what is the first – hypercortisolism with the secondary development of the metabolic syndrome or metabolic syndrome and insulin resistance that leads to adrenal proliferation as seen in polycystic ovary disease?

Despite the fact that many authors found a higher prevalence of subclinical Cushing syndrome in patients with nonfunctioning adrenal tumors, we were not able to confirm it, because there was only 4% prevalence of SCS in our cohort being lower than was the prevalence of the metabolic syndrome.

The prevalence of other endocrinopathies is in accordance with many previous studies [19, 20, 21, 22].

Despite the higher prevalence of dyslipidemias we did not find any relationship between plasma cortisol and plasma lipid values. There were no significant differences in evaluated bichemical and hormonal parameters between adrenal adenomas and other lesions . We also did not find a significant difference in evaluated data between lesions smaller than 3 cm and lesions greater than 3 cm.

The overproduction of adrenal androgens from adrenal incidentalomas is rare, because adrenal androgens overproduction is usually manifested primarily by clinical signs of an androgen excess. Routine evaluation of an adrenal androgen is not necessary [4, 23]. Only one patient in our study had DHEAS overproduction with the histological finding of an adrenal adenoma with foci of myelolipoma. However this patient did not exert clinical symptoms of an androgen excess [24].

On the other side we found a relatively high prevalence of an exaggerated response of 17 OHP after ACTH stimulation that was detected in 5% of patients. Other authors reported that the exaggerated response of ACTH is a frequent finding in patients with adrenal incidentalomas with the prevalence ranging betwen 17-71% of patients. Many of them including our patients had no clinical symptoms of steroid enzymopathy. Thus we suppose in this and in a recent study a partial blockade of 21 hydroxylase inside of the tumor [23, 25].

In this study we confirmed a higher prevalence of symptoms of the metabolic syndrome in patients with adrenal incidentalomas, which indicate systematic screening for the metabolic syndrome including evaluation of the insuline resistance in these patients.

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