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Arterial hypertension in adrenal incidentalomas

Nadciśnienie tętnicze w przypadkowo wykrytych guzach nadnerczy

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Summary

Arterial hypertension is a life threatening sign of overt Cushing syndrome. In the incidentally found adrenal tumours (adrenal incidentalomas – AI) subclinical adrenal hyperfunction sometimes has been observed; hormonally dependent arterial hypertension may have an adrenocortical origin (subclinical hypercortisolism, aldosterononism or – rarely – congenital adrenal hyperplasia, t. II) or chromaffin cell origin (pheochromocytoma). The most frequent mechanism of arterial hypertension is subclinical excess of cortisol. This study aimed at evaluation of frequency of arterial hypertension and its aetiology in a group of 2430 patients with AI (90% with probably benign tumours and 7% with adrenocortical cancer). Arterial hypertension has been noted in 1003 patients (41%), however in about 10% not exceeding 140/95 mmHg. The material has been analyzed basing on oncological and endocrinological criteria. In probably benign tumours arterial hypertension was present in 42%, while in adrenocortical cancer – in 39%. Hormonal analysis revealed pre-Cushing's syndrome in 136 patients (5.6%), hyperaldosteronism in 34 ones (1.4%) and pheochromocytoma in 65 patients (2.7%) Arterial hypertension was found in almost all patients with subclinical Cushing's syndrome, all patients with hyperaldosteronism and in about 3/4 of the patients with chromaffin tumours. In comparison with obesity and diabetes mellitus arterial hypertension was the most frequent component of the metabolic syndrome.

Key words: adrenal tumour, adrenal incidentaloma, subclinical Cushing's syndrome, arterial hypertension

Streszczenie

Nadciśnienie tętnicze jest głównym objawem zagrażającym życiu w jawnym klinicznie zespole Cushinga. W przypadkowo wykrytych guzach nadnerczy – incidentaloma nadnerczy (AI), w części przypadków obserwuje się dyskretne objawy nadmiernej sekrecji hormonalnej, najczęściej w zakresie sekrecji kortyzolu. Hormonalnie zależne nadciśnienie tętnicze może być związane z korą nadnerczy (podkliniczny zespół Cushinga, hiperaldosteronizm, albo, rzadko – wrodzony przerost nadnerczy typu II) albo z rdzeniem nadnerczy (pheochromocytoma). Najczęstszą przyczyną nadciśnienia nadnerczowo-zależnego jest podkliniczny nadmiar kortyzolu. Prezentowana tu praca miała na celu ocenę częstości występowania i etiologii nadciśnienia tętniczego w grupie 2430 pacjentów z AI, obejmującej blisko 90% łagodnych guzów i 7% przypadków raka kory nadnerczy. Nadciśnienie tętnicze odnotowano u 1003 osób (41%), jednak w ok. 10% przypadków nie przekraczające 140/95 mmHg. W prawdopodobnie łagodnych guzach nadciśnienie tętnicze stwierdzono w 42% przypadków, a w raku kory nadnerczy w 39% Analiza wyników badań hormonalnych ujawniła podkliniczny zespół Cushinga u 136 pacjentów (5,6%), aldosteronoma u 34 (1,4%) i guz rdzenia nadnercza u 65 pacjentów (2,7%). Nadciśnienie tętnicze występowało we wszystkich przypadkach z cechami podklinicznego zespołu Cushinga i aldosteronoma i w ok. 3/4 przypadków guzów chromochłonnych. Porównując częstość występowania otyłości i cukrzycy w tej grupie chorych należy stwierdzić, że nadciśnienie tętnicze było najczęściej występującą składową zespołu metabolicznego.

Słowa kluczowe: guz nadnercza, incidentaloma nadnercza, podkliniczny zespół Cushinga, nadciśnienie tętnicze

INTRODUCTION

An incidentally detected adrenal tumour (*adrenal incidentaloma* – AI) is an anatomical lesion of oncological and endocrinological significance, which constitutes a real challenge for the medical society due to the rapidly increasing frequency of its detection (1).

The literature contains a lot of reports on this subject; a few of them may be distinguished by conducting an in-depth analysis of their substantive value and considering the number of discussed cases, and these cases constitute a basis for contemporary knowledge within this area (2-6).

Hypertension belongs to the most dangerous symptoms in the clinically manifested Cushing's syndrome, due to complications that may occur. In some cases of AI, less intensively manifested symptoms of hyperadrenocorticism may occur, accompanied by hypertension of diverse intensity. It may be caused by adrenocortical function disorder (the most frequently subclinical hypercortisolemia, i.e. subclinical Cushing's syndrome, hyperaldosteronism; and the most rarely, congenital adrenal hyperplasia type 2) or by adrenomedullary function disorder (mainly pheochromocytoma).

The purpose of this paper is to evaluate incidence of hypertension in AI and aetiological profile of this phenomenon.

MATERIALS AND METHODS

Material included 2430 cases of AI, including 1782 females and 648 males (F/M ratio = 2.75), in the ages between 11 and 87 years (only 3 subjects below 18 years of age, and two of them remaining under care due to adrenocortical cancer). This group included 96 subjects (4%) below 30 years of age and 979 subjects (40%) above 60 years of age. The size of the adrenal tumours ranged from 1 cm to 25 cm in diameter. In 1626 patients (67%), the size of a focal lesion did not exceed 3 cm in diameter. Tumours were located on the right side in 1065 patients (44%), and on the left side in 841 subjects (35%); bilateral tumours occurred in 504 patients (21%).

The methods included: clinical examination, tumour imaging, hormonal evaluation and basic laboratory evaluation, as well as pathomorphological evaluation in 697 cases (30%) undergoing surgical treatment.

Clinical examination: medical interview and physical examination, blood pressure measurement, ECG, measurement of height and body weight, with BMI calculation.

Imaging diagnostics included ultrasound evaluation (traditional ultrasound evaluation, and in some cases it included administration of a contrast medium and elastography), referred to as USG; computed tomography (CT-scan), which in a majority of cases included an evaluation conducted after administration of the contrast medium; magnetic resonance imaging (MRI) mainly in cases, where differentiation between adrenal adenoma and nonadenoma was necessary; PET was performed in individual cases. Lesions established in an ultrasound evaluation conducted on an outpatient basis required confirmation in the CT-scan. Moreover, the ultrasound evaluation was used for monitoring the course of a disease. The tumour examination in CT-scan, which included an evaluation of the tumour density during the 1st phase of examination and the rate of contrast medium elimination, allowed determining relatively well, whether the lesion was benign in nature (up to 10 HU within the 1st phase of CT-scan, elimination of at least 50% of the contrast medium after 10 minutes).

Imaging diagnostics also included densitometry.

Evaluation of the adrenocortical function: determination of cortisol blood level at morning and evening (usually at 10:00 pm), i.e., checking daily rhythm of cortisol, androgens (DHEA-S, androstendion, 17OH progesterone, testosterone), plasma level of ACTH, conducting an inhibition test of cortisol secretion by administration of dexamethasone in the dose of 1 mg at 10:00 pm; content of 17-OHCS or free cortisol and 17-KS was checked in 24 h urine collection. Determination of aldosterone and PRA in blood after rest and after bringing into vertical position as well as determination of aldosterone in 24 h urine collection – were conducted, if necessary.

Evaluation of adrenomedullary function: checking content of metoxycatecholamines or metanephrines in 24 h urine collection.

Routine laboratory evaluation: complete blood count, urinalysis, blood level of calcium, sodium and potassium and elimination in 24 h urine collection (if necessary), fasting glucose level and glucose level after 1 and 2 hours following breakfast, OGTT test (if necessary), lipid profile , ESR, CRP and coagulation profile.

In patients with hypertension, evaluation of aldosterone in 24 h urine collection and aldosterone and PRA in blood were conducted after rest and in stimulation test, as well as determinations of metanephrines in 24 h urine collection. Within the period of cooperation with NIH (Bethesda, USA), series of ca. 60 plasma samples were sent for determination of metanephrines.

RESULTS

Based on the clinical picture, as well as results of imaging, hormonal and pathomorphological evaluations in **2179 cases (90%), the existence of benign lesions in adrenal glands was established; adrenocortical cancer was established in 175 cases (7%), and other malignancies** (lymphomas, malignant chromaffin cell tumours, sarcomas, ganglioneuroblastomas) in 14 cases (0.5%), **metastases to the adrenal glands** (the most frequently originaing from the renal cell carcinoma and lung cancer) in 62 cases (2.5%).

Subclinical Cushing's syndrome was diagnosed in 136 patients = in 5.6% of cases, **subclinical hyperaldosteronism in 34 patients** (1.4%), **pheochromocytoma in 65 subjects** (2.7%), **subclinical hyperandrogenism** (mainly in adrenocortical carcinoma) **in 35 cases** (1.4%).

Primary adrenocortical insufficiency (in case of bilateral metastases to the adrenal glands and lymphomas) **was established in 29 patients** (1.2%), and secondary adrenocortical insufficiency (independent from the underlying disease) **in 42 patients** (1.7%).

Obesity was established in 466 cases = in 19% of subjects.

Hypertension was noted in 1003 patients, i.e. in 41% of cases; in 102 cases, it did not exceed the value

of 140/95 mmHG, so higher values corresponded to 37% of cases. In the aetiological profile, hypertension related to 923 patients (42%) with so-called benign lesions, 68 of patients (39%) with adrenal carcinoma and 12 patients with metastases in the adrenal glands (0.5%). Hypertension existed in nearly all cases of subclinical Cushing's syndrome and aldosteronoma, and in 48 cases of pheochromocytoma (74%).

Type 2 diabetes mellitus was established in 250 patients, i.e. in 10% of cases.

DISCUSSION

Detailed discussion of the role of adrenal hormones in etiopathogenesis of hypertension was presented by Przybylski and Malendowicz in the textbook entitled "Nadciśnienie Tętnicze" ["Hypertension"] (7). Cellular activity of adrenocortical hormones is connected with presence of 2 types of receptors. Type I, defined as the mineralocorticoid receptor (MR), reveals high affinity to aldosterone and corticosterone. Type II receptor, referred to as the glucocorticoid receptor (GR), demonstrates high affinity to dexamethasone and to other glucocorticosteroids, but considerably lower to aldosterone. It is well-known that cortisol shows evident mineralocorticoid action, while aldosterone manifests no action, which is usually demonstrated by glucocorticosteroids. The effect of aldosterone and other mineralocorticoids on the cardiovascular system was presented in a separate article in this magazine, as well as pathomechanism related to adrenomedullary hormones, and for this reason, they will not be discussed in this report.

The most common form of subclinical adrenocortical hyperactivity includes discrete excess of cortisol, which manifests in an insufficient decrease of cortisol in the blood at evenings comparing to mornings. This way, the organism does not have necessary rest because of the specific effect of cortisol on the vascular system. Within the scope of comprehensive mechanism of blood pressure increase resulting from cortisol, attention is drawn to the inhibiting activity of the vessel dilatation system by influencing nitric oxide synthase, prostacyclin synthesis and kallikrein-kinin system. The renin angiotensin system is also activated. In connection with adrenomedullary hormones, reactivity of blood vessels for catecholamines increases, and their peripheral catabolism decreases, and it especially relates to normetanephrine. In case of inability to deactivate 11 beta hydroxysteroid dehydrogenase type 2 in kidneys, its higher amount reaches the mineralocorticoid receptor, and it imitates excess of aldosterone. This way, responsiveness to antihypertensive drugs is reduced, which remains until the moment when the excess amount of cortisol is reduced. It results in occurrence of thickening of the arterial internal layer as well as atherosclerotic lesions.

Similarly to the opinion dominating in the literature regarding incidence of subclinical Cushing's syndrome (2, 6), also our material shows that this type of disturbance does not exceed 6% (5.6% in the currently studied group). Higher values of this rate, especially provided in Italian literature (8), are the most likely caused by more liberal diagnostic criteria. Also the incidence of subclinical Conn's syndrome oscillating in our material at the level of 1% is closer to global papers than to the observations of Italian authors (9). It is worth mentioning that recently attention has been paid to adenomas simultaneously secreting excessive amounts of cortisol and aldosterone (10). So far, 37 similar cases have been reported all over the world.

Strict diagnostic criteria regarding the incidental nature of diagnosing an adrenomedullary tumour caused that the proportion of these cases in our material amounted only to 2.7%, even though the most frequently reported values range between 3-5%.

In contrast to cases of metabolic disorders, in our group of patients, incidentally detected adrenocortical carcinoma (7%) occurred more frequently, which resulted from relatively easy access to abdominal ultrasound evaluation, which is an excellent screening method. Incidence of hypertension in adrenocortical carcinoma (39%) was similar to its incidence in benign cases (37 to 41% depending on criterion of pressure level). In the subgroup with hypertension not exceeding 140/95 mmHg, we considered the causal role of stress in persons with labile vegetative system.

The incidence of hypertension in our group of patients with AI is clearly higher than it is in the general population reported at the level of 24.6% (11). An analysis of the aetiological profile allows believing that a causal relationship existed between hypertension and observed pathological lesion in 35% of cases.

Comparing to other symptoms of the metabolic syndrome, as obesity (incidence 19%) and diabetes mellitus (10%), hypertension was the most frequently occurring clinical symptom.

While discussing the problem of hypertension in AI, it should be emphasized that there is one threat, which was occasionally reported in clinically silent cases of pheochromocytoma after administration of glucocorticosteroids in the dose exceeding 1 mg of dexamethasone (12), in the form of severe hypertensive crisis, and even catecholamine crisis, which is also called "pheochromocytoma crisis", with life-threatening symptoms as heart failure, liver failure, renal failure and central nervous system failure. It requires taking special care while planning the performance of an inhibition test of cortisol secretion with high doses of dexamethasone in insufficiently diagnosed cases.

CONCLUSIONS

1. In our group of 2430 patients with AI, hypertension occurred in ca. 40% of cases.
2. Only in 35% of cases with hypertension, causal relationship between this symptom and lesion in the adrenal glands could be assumed.
3. Hypertension was the most frequently occurring component of metabolic syndrome, and it occurred approximately twice as frequently as obesity and 4 times more often than diabetes mellitus.

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