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Review paper

Diagnostics and treatment of adrenal tumors detected accidentally

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Abstract

Introduction: **The adrenal glands are paired and located in the retroperitoneal space, above the upper pole of the kidney.** Adrenal tumors depending on the histopathological structure, may be divided into: epithelial, mesenchymal, lymphoid and adrenal medulla tumors. Depending on the etiology, distinguishes between tumors, inflammatory tumors, true adrenal cysts, pseudocysts and parasitic adenomas and proliferative processes. The adrenal incydentaloma is a pathological tissue in the adrenal gland, with a diameter of ≥ 1 cm, diagnosed during diagnostics for reasons other than adrenal pathology.

Aim: The work aims to discuss the latest available diagnostic and therapeutic methods of incidentalomas, which are an increasing clinical problem, due to the increasing availability of imaging ultrasonography and computed tomography.

Material and methods: The paper was based on the available literature of the subject, magazines and the latest guidelines.

Results and discussion: In diagnosing adrenal tumors, imaging diagnostics (ultrasonography, computed tomography, magnetic resonance, positron emission tomography, scintigraphy, fine needle aspiration biopsy), hormonal (ACTH, cortisol, dexamethasone suppression tests, diurnal excretion of free cortisol in urine and/or 17 hydroxycorthoroids, plasma renin activity, aldosterone, dehydroepiandrosterone sulphate, androstenedione, 17-alpha-hydroxyprogesterone, chromogranin A, metanephrins in plasma and excreted in urine and biochemic. Adrenal glands may have hormonal activity: a pheochromocytoma usually produces adrenaline and norepinephrine, and rarely dopamine; adrenocortical tumors that excessive produce cortisol cause ACTH-independent Cushing's syndrome; adrenal tumors may also secrete excess aldosterone and androgens.

Conclusions: **Adrenal incydentaloma are common in everyday clinical practice** and its treatment is established on the basis of interviews, physical examination, tumor phenotype in computed tomography and tumor hormonal activity.

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1. INTRODUCTION

The adrenal glands are the endocrine glands, the paired, located in retroperitoneal space, above the upper pole of the kidney, within its adipose capsule. The adrenal glands are made of peripheral bark, taking up approximately 80%–90% of the organ and core, in the central part of the gland. The right adrenal gland is triangular in shape, located to the back of the liver, medially to the inferior vena cava. The left adrenal gland is slightly more round, it is located backwards from the stomach, from which the lesser sac separates them.[1] Adrenal tumors can come from both layers of normal adrenal glands. The division of adrenal tumors, depending on the histopathological structure, is presented in Table 1.[2–7]

Depending on the etiology among adrenal tumors, we distinguish between tumors (primary and metastatic), inflammatory (tuberculosis, sarcoidosis, histoplasmosis), true adrenal cysts, pseudocysts, parasitic adrenal cysts and proliferative processes that are characterized by microademic hyperplasia, macrogyal adrenal glands or are observed in patients with congenital adrenal hyperplasia (CAH).[3,8]

Adrenal incidentaloma (AI) is a pathological tissue mass in the adrenal gland, at least 1 cm in diameter, diagnosed during diagnostics for reasons other than suspected adrenal pathology.[4,9,10] AI diagnosis excludes focal lesions depicted during the diagnostics of hormone-dependent hypertension or active cancerous disease.[11] AI are asymptomatic in 70%–94%, benign adenomas, without hormonal activity. The adrenal carcinoma is rarely diagnosed, in about 2%–4% of patients. The risk of cancer increases with the size of the tumor. In tumors up to 4 cm the risk is about 2%. When the diameter of the cancerous change exceeds 6 cm, the risk of malignancy increases up to 25%.[2,12] In the available literature, 2.5 times more frequent occurrence of AI in women in life-related studies is noticed, whereas in post-mortem examinations there are no such differences.[13,14] These differences are probably related to the fact that women more often and more willingly submit to available imaging examinations. In addition to primary adrenal cancers, the incidentalomas may be metastatic, most commonly kidney cancer, lungs, liver, less often of colon, stomach, breast and melanoma.[11] AI may also be inflammatory or granulomatous changes in the course of tuberculosis or histoplasmosis, hematomas, cysts, lipomas, liposarcoma, schwannomas or may occur in persons with CAH.[2,4,13]

2. AIM

The increasing availability of ultrasonography (USG) and computed tomography (CT) imaging has made adrenal tumors a increasing clinical problem. Previously, adrenal tumors were diagnosed in 1.4%–6.0% of post-mortem examinations, and currently they are diagnosed in approximately 0.4% of people in abdominal ultrasound scan examinations and in 2%–4% of CT studies.[15] The work aims to discuss the available diagnostic and therapeutic methods of AI.

3. MATERIAL AND METHODS

The paper was based on the available literature of the subject, magazines and the latest guidelines (MEDLINE literature search). The search was conducted using the term 'adrenal incidentaloma'.

4. DISCUSSION

4.1. Methods for diagnosing adrenal tumors

USG is the most available, often first, study that shows the adrenal tumor. The ultrasound scan examination also reveals possible necrosis, calcifications or cysts in the tumor. It is the method of choice for further periodic check-ups in people who were excluded from hormonal and oncological indications for surgery. Due to the anatomical position, the left adrenal glands are more difficult to assess in the ultrasonography than the right adrenal glands. Tumors of about 2 cm are already well visible on both sides in this imaging method, while smaller ones are mainly seen in the right adrenal glands.[15]

CT without or with intravenous contrast evaluated after 1 and 10 minutes is a test that verifies ultrasound scan, and also the most useful for the assessment of adrenal tumor. A CT scan without contrast is the first-line examination in the diagnosis of adrenal tumors, relatively cheap. The CT examination with the use of contrast agent aims to accurately assess focal lesions inconclusive in CT studies without any contrast medium (Table 2).[16–18]

Nuclear magnetic resonance (NMR) performed in phase and antiphase with the assessment of tumor size, location and phenotype can be a complementary examination of CT, especially in cases of suspected pheochromocytoma or adrenocortical carcinoma. The NMR study differentiates adenomas from the so-called non-adenomas. This study is recommend-

Table 1. Adrenal tumors.

Epithelial	Mezenchymal	From lymphatic tissue	Of suprarenal medulla
Benign adenoma	Lipoma	Lymphoma	Chromaffin tumor
Minor tumors hyperplasia of adrenocortical glands – primary pigmented nodular adrenal dysplasia (PPNAD)	Angioma		Neuroblastoma, schwannoma
Major tumors hyperplasia of adrenocortical glands	Sarcoma		Tumors with meshwork composite: ganglioneuroma, ganglioneuroblastoma
Adrenal cortical carcinoma	Liposarcoma		

Table 2. Rated parameters.

Tumor shape and alignment with neighboring organs	Tumor densities (radiation reduction factor)	Internal structure
Benign tumors – regular shape, well separated from the surrounds	Adrenocortical adenomas / liposarcoma – negative density, tumors with a lot of adipose tissue	Benign tumors – homogeneous lesions
	Low lipid adenoma – density not more than 10 jH	Malignant lesions / pheochromocytoma – foci of decay
Malignant tumors – blurred borders, outline blurred by infiltration of surrounding organs	Suspected malignancy / pheochromocytoma of the adrenal gland – native density over 10 jH	
	After the contrast injection, significant change in intensity at 1 and 10 minutes; quick rinsing of the contrast to a value of at least 50% of the maximum value – suggestion of benign change, delayed contrast rinsing with leach rate less than 50% associated with pathological vascularization – suggestion of malignant or pheochromocytoma; lack of increased densities after contrast agent injection – cysts and hematomas	

ed for pheochromocytoma and paraganglioma (PPGL) associated with suspicion of metastases, cranial and neck basal paraganglioma, in patients with surgical clips that may be a source of artifacts in CT, pregnant women, children, people with a known germline mutation, as well as patients who have a history of sensitization to iodine contrast agents used during CT and those exposed lately to ionizing radiation.[17,19]

Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) input is used in the diagnosis of adrenal cortex cancer and metastatic changes.[20]

Adrenal scintigraphy using 131I-6-beta-iodomethyl-19-norcholesterol iodine cholesterol analogs (NP-59) is a test useful in the diagnosis of Cushing's syndrome or, more rarely, primary hyperaldosteronism, to differentiate adenoma and adrenal hyperplasia.[20] Adrenal scintigraphy with the use of 123I metaiodobenzylguanidine (MIBG) is characterized by high sensitivity and specificity in the detection of pheochromocytomas, including those located out of adrenal.[16] A fine-needle aspiration biopsy (FNAB) is performed under the control of CT. FNAB is currently rarely performed due to the high risk of complications such as: pneumothorax, kidney or liver haemorrhage. FNAB is performed mainly when suspected metastatic tumor with an unknown starting point or adrenal tuberculosis. The study is contraindicated in case of suspected adrenocortical cancer due to the risk of tumor spread and pheochromocytoma due to catecholamine crisis.[10,16,21]

Hormonal diagnosis is presented in Table 3.[6,9,10,19,22–24]

In the diagnostics of adrenal tumors, biochemical tests such as peripheral blood morphology, fasting blood serum, lipid profile, serum sodium, potassium and diurnal potassium excretion in the blood are also assessed.[9,10]

4.2. Adrenal hormone-active tumors

Phaeochromocytoma is a tumor originating from pheochromocytomas, most often the adrenal medulla (adrenal location is almost 90% of cases), usually producing adrenaline and norepinephrine, and less frequently dopamine. It occurs in 0.1% of patients with hypertension and in about 5% of patients with AI.[19,25] Typical symptoms associated with excessive secretion of catecholamines produced by pheochromocytomas are paroxysmal increases in blood pressure, often alternating with hypotension, orthostatic hypotension, tachycardia, excessive sweating, paleness of the skin, headaches. An unrecognized, clinically silent pheochromocytoma may be the cause of hypertensive crisis in patients undergoing surgery, after CT or during, and also during other medical procedures, therefore a diagnosis of pheochromocytoma is required in each patient with AI.[25]

Adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome is caused by primary excessive production of cortisol by adrenocortical tumors, in patients with bilateral adrenal corticosteroid or McCune–Albright syndrome, it occurs in 15%–20% of people.[25–28] Autonomic secretion of cortisol should be suspected in patients with AI and obesity, newly diagnosed or unstable hypertension, diabetes and osteoporosis.[29] Patients diagnosed after detection of an AI has milder hypercortisoluria than patient with ACTH-dependent Cushung's syndrome, and patient with smaller AI receive post-adrenalectomy glucocorticoid treatment for shorter periods.[30]

Hormonal diagnosis is important because subclinical hypercortisolism may increase mortality of these people due to cardiovascular diseases and increase the risk of developing diabetes.[31,32] It should be remembered that this group of patients may never develop a full-blown Cushing's syndrome.[29]

For asymptomatic AI, the morning cortisol concentration in the dexamethasone 1 mg inhibition test over 3.4 μg/dL was determined as requiring further hormonal diagnosis for hypercortisolemia (97% sensitivity and 88% specificity in the diagnosis of hypercortisolemia).[9,31] In case of diagnostic uncertainty, a corticotropin releasing hormone (CRH) test can be performed, or again a test with 1 mg dexamethasone or a 48-hour dexamethasone 2-mg inhibition test with a morning cortisol score after the test.[23,27]

Subclinical hypercortisolism or subclinical Cushing's syndrome, according to the latest guidelines of the European Society of Endocrinology (ESE), autonomic secretion of cortisol is the most frequently diagnosed hormonal disorder in AI and constitutes 5%–8%.[10,16,25,33] These patients do not have the typical clinical features of Cushing's syndrome, but only some of its clinical and biochemical abnormalities: hypertension, abdominal obesity, carbohydrate metabolism disorders, dyslipidemia and decreased bone mass. Laboratory tests in this group of patients indicate: disturbed circadian rhythm of cortisol (elevated morning cortisol with in-

Table 3. Hormonal diagnosis.

Hormonal tests	Description
ACTH concentration in the blood serum in the circadian rhythm	The most important is the morning ACTH concentration determined until 9:00.
Cortisol concentration in the circadian rhythm	Between 6:00 and 8:00, 22:00 and 24:00 in the blood serum.
Late-night cortisol concentration in saliva	Clearly reflects the concentration of free cortisol (not related to proteins), determined between 22:00 and 24:00 (available in a few centers in the country).
Dexamethasone suppression tests	1. Morning cortisol levels were assessed in serum after administration of 1 mg dexamethasone between 22:00 and 23:00. 2. Morning cortisol in the test with a dose of 2 mg dexamethasone determined after the 2nd day of the test; is performed with intake of 0.5 mg dexamethasone every 6 hours orally for 2 days or with 2 mg dexamethasone once between 22:00 and 23:00 with the assessment of morning cortisol the next day. 3. The dexamethasone 8 mg test (Liddle test) is performed by giving 0.5 mg dexamethasone every 6 hours orally for 2 days followed by 2 mg dexamethasone every 6 hours orally for the next 2 days of the test. The test requires a 24-hour urinary excretion of free cortisol before the test, on days 2 and 4 of the test. Inhibition tests with more than 1 mg dose of dexamethasone are performed after exclusion of the adrenal phaeochromocytoma.
Daily excretion of free cortisol in urine and/or diurnal excretion of 17-hydroxycorticosteroids in urine (17–OHCS)	–
PRA	Determined for the purpose of calculating the aldosterone/PRA index. PRA is measured in the morning after nighttime rest and in dynamic tests: after orthostatic posture, with furosemide (agents stimulating the release of renin). The PRA value is influenced by the time of day, the position of the body before the examination and the diet.
Serum aldosterone concentration	After nocturnal sleep and in dynamic tests (diet with high sodium content, intravenous infusion of 0.9% NaCl, fludrocortisone, captopril (aldosterone suppressants). It should be remembered that aldosterone and PRA concentrations are the effect of the time of day, the position of the body before the examination and diet.
Concentration of DHEAS in serum	Independent of the time of day, but depending on the sex and age of the patient.
Serum androstenedione concentration	Dependent on sex, time of day and phase of menstrual cycle in women; usually high concentrations are observed in adrenal cortex cancer.
Concentration of 17-alpha-hydroxyprogesterone (17OHP) in serum	Depending on the phase of the menstrual cycle in women.
Plasma chromogranin A concentration	–
Plasma concentrations of metanephrines: metanephrine, normetanephrine and 3-methoxythrine	Concentrations of metanephrines excreted with urine in at least two 24-hour urine collections. Concentration of metanephrins in serum and urine is always determined after a special 3-day elimination diet and pharmacological modification of treatment of hypertension (only alpha-blocker-doxazosin and/or calcium channel blocker verapamil are used before testing metanephrins in serum or urine)

Comments: PRA – plasma renin activity; DHEAS – dehydroepiandrosterone sulphate

sufficient reduction of nocturnal cortisol), reduced morning ACTH concentration (<5 pg/mL), increase in circulatory excretion of free cortisol in urine or 17-OHCS at the upper limit of the laboratory standard and suppression in the desamethasone 1 mg inhibition test over 1.8 g/dL.[9,29] Some studies have shown that the cortisol and ACTH ratio at 0:00 has better the diagnostic performance than nocturnal cortisol and may be a reliable parameter for subclinical hypercortisolism screening in patient with AI.[34]

Primary hyperaldosteronism (Conn syndrome) is a group of disorders resulting from inadequately high levels of aldosterone. Conn syndrome occurs in 1.6%–3.3% of people with AI, in about 10% of patients with refractory hypertension, latent Conn syndrome is observed in about 1%–5% of people with AI and less than 1% in the general population.[10,35] According to ESE recommendations, all patients with hypertension and incidentaloma should be screened for primary hyperaldosteronism.[22,31,32] Given that the diagnosis of primary aldosteronism is time consuming, costly, and tricky and necessitates specialized clinicians, laboratories, and centers, a more appropriate selection of candidates for screening should be preferred.[36]

Adrenal tumors with excessive secretion of androgens. Excessive production of androgens by the adrenal gland – dehydroepiandrosterone sulphate (DHEAS) and androstendione, is manifested by hirsutism in women, baldness in androgen-dependent regions and severe acne. Subclinical excess of androgens in AI patients occurs in about 1% of people. Significant androgenization, especially associated with hypercortisolemia, in patients with adrenal tumor suggests the diagnosis of adrenal cortex cancer, therefore the androgens listed are malignant markers.[2]

Table 4. Indications for surgical treatment.

Urgent	Oncological	Endocrinological
Symptoms of tumor bleeding (risk of bleeding into the retroperitoneal space)	Tumors sized more than 4–5 cm	Pheochromocytoma
	Tumors with native density more than 10 jH in TK and/or contrast elimination less than 50%	Primary hyperaldosteronism
	Tumors rapidly growing above 0.8–1.0 cm/year	Cushing syndrome
	Solated metastatic changes in the adrenal gland	Subclinical hyperactivity of the adrenal cortex (if it affects the general condition of the patient's health: diabetes, unsteady hypertension)
	Suspected adrenocortical cancer	

4.3. Medical treatment in people with AI

Treatment in patients with incidentaloma is based on interviews, physical examination, tumor phenotype in CT (size, native and contrast density) and tumor hormonal activity.[10] The influence of administered medications, age and concomitant diseases must be taken into account when interpreting test results.[37]

The indications for surgical treatment of patients with adrenal tumors are presented in Table 4.[9,10,38]

In patients with hormonal active adrenal gland tumors, pharmacological preparation of the patient for adrenalectomy is necessary.[39] In the case of a pheochromocytoma, treatment of at least 2 weeks with an alpha-blocker is recommended, and if it is a patient with persistent tachycardia, the addition of a beta-blocker.[17] In patients diagnosed with Conn syndrome, aldosterone antagonists – spironolactone or eplerenone – are used a few weeks before adrenalectomy.[23] Patients with Cushing's syndrome require treatment with ketoconazole or metyrapone for 3–4 weeks.[24] In patients with tumors up to 6–8 cm, surgical treatment of the adrenal tumor is performed using the laparoscopic method, in the case of tumors more than 6–8 cm or oncological indications, classical surgical approach is used.[38] There is no consensus as for AI smaller than 40 mm and hormonally inactive.[40]

4.4. Preservative proceedings in people with AI

Individuals with normal tumor hormonal activity and tumor diameter not exceeding 4–5 cm, in CT examination with native densities of negative values or not exceeding 10 jH, with high contrast rinsing coefficient (>50%), are subjected to clinical observation. Hormonal and imaging examinations are performed every 6 months, and after 2 years once a year.[9,10] There is no consensus regarding long-term observation of patients with AI and normal hormonal activity who have not undergone surgical treatment, however according to the guidelines of the Polish Endocrinological Society 'if the change in the adrenal gland does not raise oncological anxiety and does not increase in subsequent imaging studies, you can stop the control after 4 years. In further observation, the risk of transformation to malignancy is close to zero."[9] A similar position was accepted by the ESE and confirmed on retrospective cohort study.[31,41]

Recommendations of the Polish Endocrinological Society, apart from monitoring in imaging, are also recommended to repeat the basic hormonal tests – a test of inhibition with 1 mg dexamethasone and metanephrines excreted in the urine for the first 3–5 years after diagnosis.[9] The recommendations of the ESE suggest that the hormonal diagnosis should not be repeated unless the hormonal activity of the tumor was confirmed in the first hormonal examination (cortisol in the test with 1 mg dexamethasone was less than 1.8 μg/dL). The only exception are patients who have been diagnosed with autonomous secretion of cortisol and if there are new clinical symptoms of adrenocortical hormone activity (eg. hypertension or type 2 diabetes), which may arise at the different moments of follow-up.[31] Image and hormonal diagnosis are not always sufficient to diagnose and determine the character of AI and repeating them increases the cost of treatment.[40]

5. CONCLUSIONS

AI is a common clinical problem and its picture is heterogeneous. In clinical practice, however, it appears that both imaging and hormonal tests require periodic re-indications. This significantly reduces anxiety of the patient, in addition, leaving the patient in the observation allows to monitor the patient's condition and the appearance of symptoms of possible excessive tumor activity.

Conflict of interest

The authors have no potential conflicts of interest.

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