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 incidentaloma 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 hydroxycorticoids, plasma renin activity, aldosterone, dehydroepiandrosterone sulphate, androstenedione, 17-alpha-hydroxyprogesterone, chromogranin A, metanephrins in plasma and excreted in urine and biochemical. 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 incidentaloma 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.
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. 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.4,5,10 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.15 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.2,4,11

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 ultrasound 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.

<table>
<thead>
<tr>
<th>Epithelial</th>
<th>Mezenchymal</th>
<th>From lymphatic tissue</th>
<th>Of suprarenal medulla</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign adenoma</td>
<td>Lipoma</td>
<td>Lymphoma</td>
<td>Chromaffin tumor</td>
</tr>
<tr>
<td>Minor tumors hyperplasia of adrenocortical glands – primary pigmented nodular adrenal dysplasia (PPNAD)</td>
<td>Angioma</td>
<td></td>
<td>Neuroblastoma, schwannoma</td>
</tr>
<tr>
<td>Major tumors hyperplasia of adrenocortical glands</td>
<td>Sarcoma</td>
<td></td>
<td>Tumors with meshwork composite: ganglioneuromatosis, ganglioneuroblastoma</td>
</tr>
<tr>
<td>Adrenal cortical carcinoma</td>
<td>Liposarcoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**4.2. Adrenal hormone-active tumors**

Phaeochromocytoma is a tumor originating from phaeochromocytomas, most often the adrenal medulla (adrenal location is almost 90% of cases), usually producing adrenaline and noradrenaline, and less frequently dopamine. It occurs in 0.1% of patients with hypertension and in about 5% of patients with AI. Typical symptoms associated with excessive secretion of catecholamines produced by phaeochromocytomas are paroxysmal increases in blood pressure, often alternating with hypotension, orthostatic hypotension, tachycardia, excessive sweating, paleness of the skin, headaches. An unrecognized, clinically silent phaeochromocytoma 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 phaeochromocytoma is required in each patient with AI.

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. Autonomic secretion of cortisol should be suspected in patients with AI and obesity, newly diagnosed or unstable hypertension, diabetes and osteoporosis. Patients diagnosed after detection of an AI has milder hypercortisoluria than patient with ACTH-dependent Cushing’s syndrome, and patient with smaller AI receive post-adrenalectomy glucocorticoid treatment for shorter periods.

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

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 hypercortisolism (97% sensitivity and 88% specificity in the diagnosis of hypercortisolism). 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.

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%. 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-
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.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.30,35 According to ESE recommendations, all patients with hyper-
tension 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 androstenedione, 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.3

### Table 3. Hormonal diagnosis.

<table>
<thead>
<tr>
<th>Hormonal tests</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH concentration in the blood serum</td>
<td>The most important is the morning ACTH concentration determined until 9:00.</td>
</tr>
<tr>
<td>Circa daily cortisol in saliva</td>
<td>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).</td>
</tr>
<tr>
<td>Dexamethasone suppression tests</td>
<td>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.</td>
</tr>
<tr>
<td>Daily excretion of free cortisol in urine and/or diurnal excretion of 17-hydroxycorticosteroids in urine (17-OHCS)</td>
<td>–</td>
</tr>
<tr>
<td>PRA</td>
<td>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.</td>
</tr>
<tr>
<td>Serum aldosterone concentration</td>
<td>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.</td>
</tr>
<tr>
<td>Concentration of DHEAS in serum</td>
<td>Independent of the time of day, but depending on the sex and age of the patient.</td>
</tr>
<tr>
<td>Serum androstenedione concentration</td>
<td>Dependent on sex, time of day and phase of menstrual cycle in women; usually high concentrations are observed in adrenal cortex cancer.</td>
</tr>
<tr>
<td>Concentration of 17-alpha-hydroxyprogesterone (17OHP) in serum</td>
<td>Depending on the phase of the menstrual cycle in women.</td>
</tr>
<tr>
<td>Plasma chromogranin A concentration</td>
<td>–</td>
</tr>
<tr>
<td>Plasma concentrations of metanephrines: metanephrine, normetanephrine and 3-methoxytyramine</td>
<td>Concentrations of metanephrines excreted with urine in at least two 24-hour urine collections. Concentration of metanephrines 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 metanephrines in serum or urine)</td>
</tr>
</tbody>
</table>

Comments: PRA – plasma renin activity; DHEAS – dehydroepiandrosterone sulphate
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.9,10 The influence of administered medications, age and comorbidities must be taken into account when interpreting test results.9,10

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.37 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.’9,41 A similar position was accepted by the ESE and confirmed on retrospective cohort study.9,41

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
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