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ADRENAL INCIDENTALOMA (AI) – A PUZZLE NOT ONLY FOR AN ENDOCRINOLOGIST

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SUMMARY

An adrenal incidentaloma (AI) is any lesion ≥ 1 cm in diameter detected during radiological diagnostics unrelated to suspected adrenal pathology. Each case of an AI requires extended hormonal and imaging assessments to accurately determine the nature of the tumor and its hormonal activity. The frequency of this tumor's diagnostics has increased exponentially due to the continuous progress in the development of imaging methods, especially computed tomography and magnetic resonance imaging. The most common etiology of AIs are hormonally inactive adenomas of the adrenal cortex, but there are also adrenal cortex carcinomas, pheochromocytoma, metastatic or infectious lesions. In the case of confirmation of the type of lesion, the management involves adrenalectomy or a sufficiently long clinical observation. In recent years, new markers of the malignancy of AI tumors have been discovered, both in imaging and biochemical diagnostics, which is associated with improvements in the accuracy of diagnosis and patient management. The aim of this study was to describe the definition, etiology and epidemiology of AIs and to draw attention to the complexity of diagnostics and therapy of accidentally diagnosed adrenal tumors. Current publications and guidelines from scientific societies around the world were reviewed, using keywords that were compatible with MeSH.

Key words: adrenal incidentaloma, adrenal glands, tumors, adrenal cancer, pheochromocytoma

1. INTRODUCTION AND METHODOLOGY

The adrenal glands are paired endocrine glands located retroperitoneally on the upper pole of the kidney. Their anatomy was first described by Bartholomeo Eustacius in 1563, and their activity - by Thomas Addison in 1855 [1]. In the nineteenth century, Charles-Édouard Brown-Séquard, after research on small animals, stated that the adrenal glands are an organ essential for life [1]. They consist of two parts: cortical (80-90% of the gland's mass) and medullary (10-20% of the gland's mass), which differ not only in their histological structure, but also their hormonal activity [2]. Despite their small size (10-18 g), they play an extremely important role in regulating the homeostasis of the human body [2]. The adrenal cortex produces steroid hormones - mineralocorticosteroids (aldosterone), glucocorticosteroids (cortisol) and small amounts of androgens (dehydroepiandrosterone). The adrenal medulla is responsible for the release of mainly adrenaline and, to a lesser extent, norepinephrine. Due to the wide hormonal profile, the pathology of this organ may lead to the development of many disease entities with effects on the entire organism. One of such pathological changes of the adrenal gland is incidentaloma - a tumor found accidentally, "incidentally", most often during imaging examinations of the abdominal cavity for other reasons [3]. Detection of this change is more and more frequent due to the continuous development of imaging methods of the human body - currently over 80 million computed tomographs are performed in the USA and about 5 million in Great Britain [1,4]. For this reason, they are referred to as "diseases of the modern technology" [8]. In most cases, these tumors are benign and do not require further interventions, apart from routine checks. However, due to the risk of adrenal cortex cancer, it is necessary to perform a comprehensive differential diagnosis of the lesion, taking into account both its appearance and the effect on the adrenal hormonal function [1].

The aim of this study is to present the epidemiology, diagnostic principles and procedures in the event of an adrenal incidentaloma in a patient. A review of current publications and guidelines of internal medicine and endocrinology societies from many countries of the world from 2007-2022, available in the online scientific databases of PubMed, Google Scholar and MedRxiv, using keywords compatible with MeSH.

2. DESCRIPTION OF THE STATE OF KNOWLEDGE

2.1. DEFINITION AND ETIOLOGY

The term "incidentaloma" of the adrenal glands was first used in 1982 by Geelhoed and Druy, who predicted that this issue would be a kind of challenge for future generations due to the dynamic development of imaging techniques [12]. After many attempts, the current definition of this entity comes from the 2016 guidelines of the European Society of Endocrinology and the European Network for the Study on Adrenal Tumors (ESE / ENSAT). An adrenal incidentaloma (AI), by definition, is a clinically silent lesion, most often located in the cortical layer of the left adrenal gland, visible on radiographs performed for reasons other than this organ disease [3,5]. In the current guidelines, only a tumor with a size of at least 1 cm can be defined as an AI [6]. This limit is arbitrary; however, reviews of clinical data do not indicate the need for a more detailed diagnosis of lesions below 1 cm in diameter, due to the low risk of malignant tumor and adrenal gland dysfunction [5,6]. Lesions of such small size occur in even 65% of adrenal glands examined post-mortem [17]. The term "incidentaloma" also cannot be a specific change found in the screening of patients suffering from genetic syndromes in the course of which an adrenal tumor may develop, such as von Hippel-Lindau syndrome, MEN2A and MEN2B, Sturge-Weber syndrome or neurofibromatosis [6,7]. Imaging performed to determine the malignancy and extent of metastasis of extra-adrenal tumors is also

an exclusion criterion for diagnosis [6]. Radiological features presented in Table 1 are used in the diagnosis of tumors in adults. They are not useful in the paediatric population due to the different nature of the tumors.

Table 1. Criteria used in the diagnosis of adrenal incidentalomas in adults [6,7].

1. Lesion diameter >1cm (between 1 and 4 cm)
2. Tumor density on computed tomography (CT) without contrast enhancement <10 HU
3. Contrast agent washout >50% after 10 min
4. Tracer uptake volume on scintigraphy using cholesterol analogues labelled with radioactive iodine ¹³¹ I or selenium ⁷⁵ Se

The vast majority of AI-type lesions in adults are benign adrenal adenomas (average 80%, 33-96%), most often hormonally inactive (average 75%, 71-84%). Cortisol-secreting adenomas account for an average of 12% (1-29%) of hormonally active adenomas, and aldosterone-secreting adenomas – for an average of 2.5% (1.6-3.3%) [6]. Pheochromocytoma tumors account for approximately 5-7% of all incidentalomas [3,6]. On average, adrenal cortex cancer affects 8% of cases, and metastatic lesions (most often lung, breast, kidney, melanoma, lymphoma) - 5% [3,6]. In autopsy examinations, the percentage of adenomas is significantly lower, averaging 55% (49-69%) with an increase in the percentage of cancer to approx. 10% and pheochromocytoma to approx. 11% [6]. The vast majority of lesions are unilateral (85%), bilateral lesions are mainly metastases and tuberculosis [3]. Among hormonally active tumors, the most common is pheochromocytoma (52.2%) [11]. In the pediatric population, the diagnosis of incidentaloma is actually incidental, found much less frequently than in adults [6]. The most frequently found tumor is malignant neuroblastoma (approx. 30%) [7]. Adrenal cancer is four times more frequent than a benign lesion and is hormonally functional [7]. Benign tumors, accounting for about 70% of incidentalomas, are mainly ganglioneuromas (23%), cortical adenomas (15%) and cysts (11.5%) [7]. In view of the diagnostic and therapeutic problems, a mnemonic, the so-called "the rule of four", presented in Table 2, has been proposed to better learn and remember the characteristics of adrenal incidentalomas.

Table 2. „The rule of four” [4].

1. Adrenal incidentalomas are found on average in 4% of CT examinations.
2. 4% of these are pheochromocytomas or adrenocortical carcinoma.
3. A lesion greater than 4 cm in diameter is an indication for surgical resection.
4. Monitoring of inoperable incidentalomas should last 4 years.

When defining adrenal incidentalomas, it is also worth defining the meaning of the concept of autonomic cortisol secretion (ACS). ACS designates a cortisol concentration after a 1 mg dexamethasone suppression test (DST) >1.8 µg/dl (possible) or >5 µg/dl (confirmed) in patients with adrenal incidentalomas without catabolic symptoms of Cushing's syndrome [9]. The term ACS is considered more appropriate in the context of the adrenal tumor lesions in question than the once used term subclinical Cushing's syndrome [6]. It was decided to change these wordings due to a different symptom panel in ACS than in typical Cushing's syndrome, mainly the lack of muscle atrophy and skin lesions [6].

2.2. EPIDEMIOLOGY

Adrenal incidentalomas most often occur unilaterally (85%), mainly in the cortical layer of the organ [3,6]. The diagnosis affects approximately 2% of the general population and up to 7% in the elderly population (>70 years of age), representing a common endocrine problem [1]. The incidence of this lesion varies according to the age of the patient and the type of examination performed. In autopsy studies, AIs are found in <1% among young people, about 3% in middle-aged adults and in >15% of seniors over 70 years of age. On radiological examination, AI-type lesions are found in 2-4% of middle-aged people and >10% of seniors [5]. The mean age of onset is in the 5th-6th decade of life, according to Golkowski et al. it is 56.8 ± 12.7 years [1,11]. In the population of oncological patients, these lesions give way to other diseases, accounting for 1.3-4% of cancers [10]. ACS affects 10-50% of patients with this diagnosis [1,16]. The authors of the publications agree that the frequency of diagnosis increases with age [1,6,13]. However, conflicting data concern the epidemiology of incidence by patient gender. Ceccato et al. and Goh et al. and most studies from the 20th century report that the lesion is slightly more common in women, Mantero et al. typify men as a more common group, and Lee et al. and Sherlock et al. indicate no gender dependence of incidence [1,5,13,14,15]. The likelihood of changes in the adrenal gland is also greater in obese people with diabetes and hypertension [3]. The risk of an adrenal incidentaloma being a malignant lesion is higher in younger individuals, those with a history of extra-adrenal tumors, patients with large adrenal tumours with indeterminate imaging characteristics and in bilateral adrenal tumors [16]. The average size of the lesion is 30 mm (8-230 mm) [1]. Malignant tumors in the majority of cases reached a diameter of >4 cm, with an indicated risk of tumour growth within 1, 2 and 5 years of 6%, 14% and 29%, respectively [13]. Most commonly, the lesion is localised unilaterally, with older studies (Ambrosi et al., Kasperlik-Zaluska et al., Tsvetov et al.) indicating a higher incidence in the right adrenal gland and more recent studies (Cho et al., Ahn et al., Goh et al.) suggesting a higher incidence in the left adrenal gland [1,15,17,18]. This may be due to easier anatomical access for the radiologist to the organ on the left side and a specific diagnostic error due to less frequent diagnosis of right-sided incidentalomas until they reach >30 mm in size, when their detection rate increases statistically significantly [19]. Left-sided adenomas are more common in women with a lower BMI value and in those with a history of peripheral arterial disease, including stroke [19].

In the paediatric population, the diagnosis of incidentalomas is much rarer. These tumors account for 0.04% of all tumors diagnosed in children [7]. They occur significantly more frequently among newborns and infants than in older children. It is also worth noting the different etiology of incidentalomas compared to the adult population. Tumors in children are predominantly of medullary origin, hence are much more often hormonally active and malignant [7].

2.3. DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Radiological examinations often reveal the presence of adrenal incidentalomas. Despite its mostly benign nature, there is a risk of a malignant or hormonally active lesion, which would have long-term health consequences for the patient. Therefore, any incidentaloma-type lesion should undergo thorough clinical, biochemical and imaging diagnosis to determine the potential malignancy of the tumor and the hormonal activity of the tissue, which has implications for

further appropriate treatment or observation of the patient [13,20]. In each case, the possibility of hyperactivity of the adrenal cortex - hypercortisolemia, hyperaldosteronism or of the adrenal medulla - pheochromocytoma should be considered [21].

CLINICAL EXAMINATION. The first, key diagnostic element should be the endocrine anamnesis [21]. The patient's medical condition and changes they observe in themselves may suggest the corresponding nature of the endocrine disorder. The finding of abdominal obesity, diabetes or pre-diabetes, hypertension, osteoporosis suggests ACS. Far less commonly, an AI presents in the form of overt Cushing's syndrome with 'buffalo neck', muscular atrophy and skin changes [7,21]. The presence of sudden or severe headache, weight loss, anxiety attacks, sweating, cardiac arrhythmias, palpitations raise the diagnosis towards pheochromocytoma. In contrast, the presence of hypertension, fluid retention or a history of hypokalemia directs the diagnosis towards hyperaldosteronism. Additionally, adrenal cortex carcinomas, as tumors are usually large, in about 30% cause a number of symptoms of a local mass effect, such as abdominal pain or pressure on adjacent organs, which impair their function [1]. Adrenal metastases, in addition to their characteristic bilateral presentation, may also present with symptoms of adrenal insufficiency, such as fatigue, anorexia, nausea and vomiting, orthostatic hypotonia, hyponatremia and hyperkalemia [1]. The physical examination should be based on the measurement of blood pressure and peripheral pulse, as well as looking for the above-mentioned features [21]. Unfortunately, the majority of AIs cases present without obvious clinical symptoms, which further complicates differential diagnosis and necessitates thorough imaging and laboratory investigations [7].

RADIOLOGICAL EXAMINATION. Abdominal ultrasonography (USG) is often the first step to the diagnosis of an AI. Due to their small size, adrenal glands are not visible on routine ultrasound [10]. Their size in adults should not exceed 2-5 cm, so any lesion causing enlargement of the organ should draw the sonographer's attention [10]. The sensitivity of ultrasound in the diagnosis of AIs is 76%, with the specificity of 92% [1,10]. This method allows the evaluation of calcifications, cysts or necrotic foci [17]. Any patient diagnosed with an AI on ultrasound should undergo thorough CT or MRI scan to determine the nature of the lesion [6,10]. CT examination is a mandatory first-line diagnostic tool for AIs [10]. It is accepted that MRI has no advantage over CT, with the exception of pheochromocytoma, which shows a very characteristic image on MRI [21]. Hence, it is performed when a pheochromocytoma-type lesion is suspected, when the diagnosis is uncertain after CT imaging or when there are contraindications to CT imaging (e.g. pregnancy) [17]. The size of the lesion, the X-ray attenuation coefficient (so-called 'density'), the homogeneity of the tumor, the presence of calcifications or retrograde lesions are analysed [10]. The CT protocol primarily includes a high-resolution single-phase study (layers <3 mm) or an examination with the use of an intravenous contrast agent with layers every 3-5 mm, allowing imaging of lesions as small as 5mm [17]. Most adrenal tumors can be differentiated on CT scan, except for pheochromocytoma, which is referred to as a 'radiological chameleon' due to the multitude of appearance possibilities [10]. The differentiation of lesions on CT examination is shown in Table 3.

Table 3. Radiological features of the different types of adrenal tumors [22].

Feature	Adenoma	Carcinoma	Pheochromocytoma	Metastases
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shape	round/oval	irregular	round/oval	irregular/round
demarcation	clear	blurry/clear	clear	blurry/clear
structure	homogeneous	necrosis, calcifications	homogeneous (smaller tumors), non-homogeneous (larger tumors)	
„density”	<10 HU	>10 HU (>30 HU)		
washout of contrast agent	≥ 50% in 10 min	usually < 50% in 10 min		
lipid content (MRI)	high	absent/small		
progression of the lesion	no or slow growth	fast or very fast growth	slow growth, faster than in adenomas	usually fast growth

In the diagnosis of AIs, nuclear medicine tests are also used, which, although more expensive and less available, are characterized by the highest sensitivity and specificity [1]. PET-CT examination with the use of 18-fluorodeoxyglucose (18-FDG) is most often used in the diagnosis of metastases to the adrenal gland (sensitivity and specificity of 92%). Adenoma-type lesions may result in a false positive [1]. The diagnosis of active adenoma and adrenal cortex cancer is possible by the use of ¹³¹I-6-iodomethylnorcholesterol (NP-59), which is accumulated bilaterally in healthy adrenal glands, and unilaterally in these lesions [17]. Scintigraphy with ¹²³I-MIBG or ¹³¹I-MIBG is used in the diagnosis of pheochromocytoma [22]. After the diagnosis of an AI is made, follow-up may be necessary [13,22]. The guidelines state that in the case of a diagnosis of a benign lesion with a diameter of less than 4 cm, radiological monitoring of the patient is not required [1]. The mean tumor growth is 2 mm over a median of 52.8 months [23]. Size enlargement by more than 1 cm was observed in 2.5% of cases, but none of them led to the development of adrenal cancer [23]. Larger lesions of a clearly benign nature should be reassessed after 6-12 months in order to determine the lesion severity [1]. If the diameter remains unchanged for one year, further checks may be waived [13].

HISTOPATHOLOGICAL EXAMINATION. Radiological examinations in 30% do not allow a confident differential diagnosis of adenoma from non-adenoma [4]. Fine needle aspiration biopsy (FNA) is performed in the case of tumor metastasis of unknown primary point, lymphoma or adrenal tuberculosis [22]. Contraindication to biopsy is adrenal cortex cancer (high risk of dissemination) and pheochromocytoma (high risk of hemodynamic instability), hence its limited role in diagnostic procedures [1,10]. The diagnosis of many malignant lesions is made only at the time of surgical resection and histopathological examination as its consequences [6,22].

ENDOCRINOLOGICAL EXAMINATION. In order to determine the hormonal activity of an AI, especially in the presence of the aforementioned features of endocrine disorders in the history and physical examination, it is necessary to conduct biochemical tests. For hypercortisolemia, a cortisol suppression test after oral administration of 1 mg of dexamethasone (result <1.8 µg/dl excludes hypercortisolemia, the result > 5 µg/dl implies a high probability, and with AI the specific cut-off point is 3.4µg / dl), daily excretion of free cortisol in the urine (1.5 times the upper limit of normal), serum cortisol concentration in the late evening (23.00 or 24.00) (in hypercortisolemia it exceeds 5.4 µg/dl) are performed. Additionally, the morning concentration of ACTH can be determined (with ACS <5 pg/ml). The diagnosis of ACS requires the consolidation of the clinical picture with laboratory tests [1,22]. Recognized screening tests for pheochromocytoma are the 24-hour urinary excretion

of fractionated methoxycatecholamines and the determination of the concentration of free methoxycatecholamines in plasma using high-pressure liquid chromatography (HPLC) [22]. Daily tests of the excretion of unfractionated methoxycatecholamines in the urine are often performed in Poland, but it is not recommended in the diagnosis of this tumor [22]. Additionally, it may be useful to determine the level of chromogranin A (CgA) in plasma or serum, which, however, is associated with a relatively high risk of obtaining a false positive result [1,22]. If hyperaldosteronism is suspected, the plasma aldosterone-renin ratio (ARR) is assessed, the calculation of which is based on the concentration of aldosterone and plasma renin activity. The diagnosis of primary hyperaldosteronism is supported by the presence of ARR > 30 and aldosterone levels above 10–15 ng/dl [22]. Also in this case, attention should be paid to the potential false positive results and drug interactions (progestogens, thiazide diuretics) [10,22]. If adrenal cancer is suspected, it is also necessary to determine the concentration of adrenal androgens and progesterone, the changes of which are most often visible in the presence of this adrenal gland lesion [13,22]. Annual endocrine control is recommended within 5 years from diagnosis, in the case of an AI with a diameter greater than 3 cm, due to the possibility of transformation of an inactive tumor into a functional one, and the probability is 3.8% within a year and 6.6% within 5 years. Most of these tumors cause asymptomatic hypercortisolemia [13].

Based on the above data, it can be seen how complicated AIs diagnostics can be and how multidisciplinary this diagnosis is.

2.4. TREATMENT

After the differential diagnosis has been performed and the nature and hormonal activity of the lesion have been determined, the therapeutic process should begin, which, depending on the appropriate diagnosis, will look different. Even patients with mild and inactive AI may develop cardiovascular complications (64%), pre-diabetes or type 2 diabetes (28%), obesity (41%), dyslipidemia (34%), osteoporosis and vertebral fractures (46- 82%), caused by trace amounts of secreted cortisol [16,23]. The basic method of treating adrenal tumors is surgical removal after appropriate preparation of the patient [22]. The indications for the procedure can be divided into two groups - oncological and endocrinological, which are listed in Table 4.

Table 4. Indications for the surgical treatment of AIs [1,22].

Oncological indications	Endocrinological indications
a tumor with features of a non-adenoma in imaging tests (<i>basic criterion</i>)	all cases of pheochromocytoma
<i>Subsidiary criteria:</i>	ACTH-independent Cushing's syndrome
	primary hyperaldosteronism (Conn's syndrome)
	hyperandrogenization syndrome
<ul style="list-style-type: none"> • tumor size > 5 cm • fast or very fast tumor enlargement (> 5-8 mm or 20% within a year) 	

It should be remembered that the indications for surgical treatment should be considered individually, and the above indications are only a clinical tip [22]. Surgery is most commonly performed using laparoscopic surgery from lateral or posterior access (85% of procedures) [1,4,22]. The indications for open adrenalectomy are: large tumors (> 8 cm), invasive adrenal carcinoma (risk of dissemination) and adrenal reoperation [4,22]. The most common type of

adrenalectomy is total removal of the affected organ. Sparing procedures are performed in the case of bilateral lesions, the presence of adrenal cysts or in patients with MEN2A/2B syndromes [22].

Waiting posture and clinical observation are recommended in patients for whom surgical treatment has not been established. The length and principles of this observation vary between Polish, European, American and Asian guidelines [1,13,22]. All authors agree that the control should include radiological examinations (USG - especially on the right side, or CT, in younger patients the advantage of MR over CT is a lower radiation dose) in order to monitor the progression of the lesion and endocrinological assessment [1,6,13,22]. European guidelines do not recommend AI control, in which there is no doubt that they are benign lesions <4 cm in diameter with no endocrine function [1,6]. In other cases, checks are recommended for 4-5 years every 6-12 months [1,13]. On the other hand, Polish guidelines recommend imaging examinations every 12 months for a period of 4 years in the case of undoubtedly benign lesions <3 cm, and every 3-6 months and then 12 months if the tumor is larger or raises diagnostic doubts [22]. European guidelines do not recommend re-testing of hormones in patients with no endocrine abnormalities at the initial assessment, unless new clinical symptoms of excessive secretion of adrenal hormones or worsening of comorbidities develop [6]. The Polish guidelines are more detailed and recommend a selective hormonal assessment every 12 months by conducting a test with 1 mg of dexamethasone and possibly screening for pheochromocytoma for 3-5 years [22]. As with the qualification for surgery, the conditions of clinical observation of the patient should be regulated on a case-by-case basis [22].

3. CONCLUSIONS

Adrenal incidentaloma is a common endocrine diagnosis all over the world. It is difficult to find a second such heterogeneous disease entity, which is by definition randomly diagnosed, the differentiation and treatment of which are multifaceted, and which includes both benign and non-functional tumors, as well as malignant neoplasms causing hyperfunction of the adrenal cortex or medulla. Due to this varied course, researchers from around the world are developing guidelines for the management of AIs, but further analyzes are still needed to better understand this disease, as well as to create universal therapeutic principles. The diagnosis and further differentiation of AIs is a puzzle for clinicians, not only endocrinologists, but also radiologists, surgeons and pathomorphologists. Proper management involves the cooperation of all specialists in order to make the final diagnosis and conduct patient therapy, which, due to the diversity of the clinical, radiological and histological features, must be individualized for each case.

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