MATUSZEK, Małgorzata, MAGDALENA WOŹNIAK and WIKTOR BIŁAT. Uncovering Adrenal Incidentalomas – the role of imaging methods in diagnostic process. Journal of Education, Health and Sport. 2024;68:54978. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.68.54978
https://apcz.umk.pl/JEHS/article/view/54978

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 07.09.2024. Revised: 17.09.2024. Accepted: 21.09.2024. Published: 24.09.2024.

Short Article

Uncovering Adrenal Incidentalomas – the role of imaging methods in diagnostic process

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Abstract

Introduction and purpose

An adrenal incidentaloma is any lesion found unexpectedly during an imaging study performed for an unrelated reason. The detection rate of incidental adrenal tumors is steadily increasing. The clinical presentation of these tumors is influenced by the specific hormones production, which are determined by their origin. Most lesions are hormonally inactive and may go undetected by physicians, although some can be malignant. The aim of this work is to summarize the utility of different imaging modalities in clinical practice.

State of knowledge

All adrenal incidentalomas have to undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign or if there are some malignant features. Noncontrast computed tomography is the primary imaging technique used to evaluate adrenal lesions based on their size, structure, and density. It is worth remembering that density <10 HU and homogenous appearance is consistent with a benign adrenal mass and no further imaging is required. When additional diagnostic clarification is needed, especially in malignancy suspicion, magnetic resonance imaging with a chemical shift technique should be conducted and it may be followed by nuclear medicine methods.

Conclusions

Imaging methods play crucial role in diagnostic process. Imaging studies provide easy follow-ups and allow to avoid unnecessary adrenalectomies and its complications. Therefore, they contribute to optimizing patients' health management.

Keywords: adrenal gland; adenocarcinoma; pheochromocytoma; imaging methods; computed tomography

1. Introduction

An incidentaloma refers to any pathological mass in the adrenal gland, larger than 1 cm in diameter, that is discovered unintentionally during imaging examinations conducted for unrelated reasons, typically during chest or abdominal scans [1, 2]. The diagnosis of this condition has significantly increased in recent years, primarily due to the widespread availability and advancements in imaging techniques. However, it is crucial to note that an adrenal incidentaloma is not a definitive diagnosis; it requires a personalized, comprehensive evaluation that includes clinical assessment, hormonal testing, and imaging studies to determine both the functional status of hormone secretion and the potential for malignancy. Therefore, the detection of an incidentaloma necessitates a thorough clinical evaluation, including physical examination and biochemical and functional tests, to identify any symptoms associated with excess adrenal hormones. Additionally, any such tumor, usually detected incidentally, indicates the need for further imaging diagnostics, such as computed tomography (CT) or magnetic resonance imaging (MRI), specifically targeting the adrenal glands to establish a differential diagnosis and further management [2, 3].

2. Epidemiology of Adrenal Tumors

A study conducted between 1982 and 2019 reported the incidence of incidentalomas on CT scans ranging from 0.6% to 5.1% [3]. The current increase in incidence is likely due to improved access to imaging studies and more advanced diagnostic methods compared to earlier years. The incidence also tends to rise with age, peaking in the fifth and sixth decades of life[3, 4, 5]. No significant prevalence has been observed concerning gender, chronic diseases, or genetic and environmental factors [6]. CT scans have shown a similar distribution of lesions between the right and left adrenal glands [3]. Among all adrenal tumors, non-functioning adenomas are the most common, followed by hormonally active adenomas. Among the latter, those producing glucocorticoids, leading to symptoms of ACTH-independent Cushing's syndrome, and pheochromocytomas originating from adrenal medullary cells, are the most prevalent [5, 6]. Conversely, adrenal carcinoma, aldosteronoma, myelolipoma, and metastatic tumors are much less frequent. A study by Young WF Jr. in the United States found adrenal metastases in 2.5% of patients. That was confirmed by a Polish study involving 1,444 patients with incidentalomas reported a rate of 3% [7, 8].

3. Clinical Presentation

Incidental adrenal tumors are most often clinically silent, presenting with normal adrenal function and no signs of hormone excess. Only a minority exhibit hormonal activity [9]. When they are active, symptoms vary depending on the origin of the tumor (which may arise from any of the three layers of the adrenal cortex or the medulla), manifesting as excess in glucocorticosteroids, mineralocorticosteroids, androgens, or catecholamines. Symptoms of hypercortisolemia are often evident during a physical examination, including central obesity, a rounded and flushed face, red striae on the abdomen and thighs, thinning of the skin, and proximal muscle weakness [10]. Other metabolic complications may include hypertension, osteoporosis, and impaired glucose tolerance. Hyperandrogenemia associated with adrenocortical carcinoma may present as virilization in women, hirsutism, increased acne, and reduced libido [11]. These symptoms may necessitate a differential diagnosis to exclude conditions such as polycystic ovary syndrome and congenital adrenal hyperplasia, which can occur independently of an adrenal tumor. Hyperaldosteronism can be challenging to diagnose due to the lack of distinctive phenotypic features. Hypertension resistant to antihypertensive therapy, often accompanied by hypokalemia (manifesting as muscle weakness, paresthesias), arrhythmias, edema, increased thirst, and frequent urination, can be helpful clues [12]. The clinical presentation of pheochromocytoma results from excessive stimulation of the sympathetic nervous system by catecholamines secreted by tumor cells, with the most characteristic symptom being hypertension, which may occur in paroxysmal episodes or be less noticeable [13].

4. Diagnostics

4.1 Hormonal Testing

Determining the hormonal activity of adrenal incidentalomas is crucial for guiding therapeutic management. Diagnosis typically begins with basic screening tests, followed by specific examinations and functional tests if symptoms of hormone excess are present or screening results are positive. For hypercortisolemia, diagnostic evaluation begins with measuring cortisol rhythms and 1 mg dexamethasone suppression test is recommended. The measurement of catecholamine metabolites (methoxycatecholamines) in plasma or a 24-hour urine collection is considered to be the most useful for diagnosing pheochromocytoma. Screening tests for hyperaldosteronism include assessing hypokalemia and the plasma aldosterone-renin ratio. For diagnosing hyperandrogenemia, measurements of dehydroepiandrosterone sulfate (DHEA-S), 17-OH progesterone, and total testosterone are recommended. Interpretation of these test results is beyond the scope of this article [2, 3, 5, 6].

4.2 Imaging Studies

The primary objective of imaging studies is to distinguish benign adenomas from malignant lesions, such as adrenal carcinomas or metastatic tumors. It is also important to recognize that pheochromocytomas, which are typically benign, display characteristic morphological features identifiable through imaging. CT and MRI are the most commonly used modalities to exclude malignancy. Less commonly, fluorodeoxyglucose positron emission tomography (PET-FDG) is used to directly confirm a malignant process [14]. A high-resolution (<3mm) single-phase CT scan of the adrenal glands without contrast administration is suggested as the first imaging modality [2]. This scan provides information about the tumor's phenotype, including its size, borders, homogenicity and density measured in Hounsfield units (HU). Adenomas typically exhibit the following characteristics on CT: size < 4 cm, regular, well-defined borders, homogeneous structure without calcifications or hemorrhage, density less than 10 HU, attributed to the lipid-rich structure [3]. However, according the 2023 European Society of Endocrinology guidelines, the size criterion (<4 cm) has been removed, and it is now advised not to perform additional imaging follow-up for homogeneous adrenal masses with ≤10 HU, irrespective of size [2] On the other hand, benign tumors may exceed 4 cm in size; if the density is less than -20 HU, this suggests a less common benign tumor, such as a myelolipoma [5, 9]. The size, homogenicity and density are key factors in interpreting results, as lesions larger than 4 cm are associated with an increased risk of adrenal cancer [4, 7]. A density greater than 30 HU strongly indicates malignancy, such as a carcinoma or pheochromocytoma. However, it is essential to consider poor-lipid adenomas, where the density may exceed 10 HU. Although contrast-enhanced imaging carries a higher systemic burden, it is often employed as the first-choice method for imaging adrenal incidentalomas, particularly when the density falls between 10 and 30 HU, and the tumor's nature is uncertain. In such cases, a biphasic CT scan with iodine contrast may be indicated, which includes assessments at baseline, 1 minute (enhancement phase), and 10 or 15 minutes after (washout phase). These values help calculate the "washout factor" [1, 5]. Adenomas are characterized by rapid contrast uptake and washout, distinguishing them from malignant tumors [2]. Tumors with a washout rate >50% at 10 minutes after contrast administration are typically adenomas, whereas a delayed washout rate (<50%) may indicate adrenal cancer, pheochromocytoma, or metastasis [3]. Imaging features indicative of malignancy include: size > 4 cm, irregular borders, heterogeneous internal structure (possible necrosis, hemorrhage, calcification), density above 10 HU, usually > 30 HU, washout rate <50% [6, 10, 15]. Pheochromocytomas, called „radiological chameleons”, though typically

benign, exhibit varied imaging features [16]. Their size and shape are not diagnostic criteria; however, they are often large at diagnosis. Their structure may be heterogeneous or, less commonly, homogeneous, with solid, cystic, and/or calcified areas. Pheochromocytomas typically enhance strongly and rapidly on biphasic CT scans, with a washout rate usually less than 50%, similar to malignant lesions, although adenoma-like washout patterns are also observed, confirming their imaging variability [1, 10]. For metastatic tumors, which are often bilateral, imaging aims to identify the primary tumor site. Adrenal metastases most commonly originate from lung, kidney, colon, breast, esophagus, pancreas, liver, stomach cancers, as well as melanomas, leukemias, and lymphomas. MRI may be helpful in ambiguous cases, particularly when contraindications to X-ray exposure exist, such as pregnancy or iodine contrast allergy. MRI involves obtaining T1- and T2-weighted images and utilizes the chemical shift technique to assess lipid content in adenoma cells rich in fat [3, 17]. In chemical shift imaging, lipid-containing lesions (adenomas) show reduced signal intensity on out-of-phase images compared to in-phase images, appearing hypointense. The accuracy of detecting adrenal tumors using this method is estimated at 95-98% [18]. Poor-lipid adenomas, which are difficult to visualize on CT, also display this distinguishing feature, as do pheochromocytomas, which typically have high signal intensity [19]. MRI has an estimated sensitivity of around 90% for diagnosing lipid-rich adenomas [1]. Assessing lipid content helps differentiate pheochromocytomas from adrenocortical carcinomas, as the latter contain trace amounts of lipids [17]. Patients whose diagnosis remains inconclusive after CT and MRI may undergo further evaluation using nuclear imaging techniques to assess cellular metabolism dynamics. PET is often employed for this purpose. The most common PET tracer, flurodeoxyglucose (FDG), an analog of glucose, helps assess the metabolic activity of cells in an adrenal lesion. FDG-PET is useful when other imaging modalities cannot clearly identify malignancy [4]. This test has moderate sensitivity; however, some adrenal adenomas and pheochromocytomas may yield false positives. The sensitivity of this method is estimated at 100%, with a specificity of 80-100% for differentiating malignant from benign lesions [1, 20]. Another radionuclide used in malignancy diagnosis is metaiodobenzylguanidine that is an analog of norepinephrine. This iodine-labeled radiopharmaceutical is used in imaging adrenal pheochromocytomas, with increased uptake by tumor cells [21]. Methahydroxyephedrine, another substance used in diagnosing pheochromocytomas, offers more reliable results than other metaiodobenzylguanidine forms, but its short half-life limits its use [22].

5. Summary

The incidental discovery of adrenal tumors has become more common due to the greater availability of imaging studies and advances in whole-body imaging techniques. Any incidentaloma warrants a comprehensive clinical evaluation, including hormonal and imaging studies, to assess tumor function and potential malignancy. The primary benefit of imaging studies is their ability to initially differentiate benign or malignant tumors, whether primary or metastatic. Thus imaging studies remain an essential part of incidentalomas' diagnostic process and are crucial for appropriate management.

Conceptualization, MM, MW, WB; methodology, MM, MW, WB; software, MM, MW, WB; check MM, MW, WB; formal analysis, MM, MW, WB; investigation, MM, MW, WB; resources, MM, MW, WB; data curation, MM, MW, WB; writing - rough preparation, MM, MW, WB; writing - review and editing, MM, MW, WB; visualization, MM, MW, WB; supervision, MM, MW, WB; project administration, MM, MW, WB. All authors have read and agreed with the published version of the manuscript.

Funding: This research received no external funding. Institutional Review Board Statement: Not applicable. Informed Consent Statement: Not applicable. Data Availability Statement: Not applicable. Acknowledgments: Not applicable. Conflicts of Interest: The authors declare no conflict of interest.

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