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Review article

Adrenal incidentalomas: A guide to assessment, treatment and follow-up

Stavroula A. Paschou[a,b], Andromachi Vryonidou[b], Dimitrios G. Goulis[a,*]

[a] Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
[b] Department of Endocrinology and Diabetes, Hellenic Red Cross Hospital, Athens, Greece

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ABSTRACT

Adrenal incidentalomas are clinically unsuspected lesions that are detected in adrenal glands during imaging procedures for other causes. With widespread use of imaging – both computed tomography (CT) and magnetic resonance imaging (MRI) – adrenal incidentalomas are now a common clinical problem. The two main clinical issues to be determined in this setting are the risk of malignancy and the hormonal activity of these lesions. The answers to these two questions, along with the clinical characteristics of each individual patient and co-morbidities, will guide the treatment strategy, which can vary from simple follow-up to surgical resection. The objective of this article is to present updated information on the definition, prevalence, imaging and functional features of adrenal incidentalomas and to provide a guide to their optimal assessment, treatment and follow-up. This review collected, analyzed and qualitatively re-synthesized information regarding: (1) the various clinical entities known as "adrenal incidentalomas", (2) the initial assessment of risk of malignancy, (3) the initial assessment of whether the lesion is hormonally active or non-functioning, (4) the absolute and relative indications for surgical treatment, (5) the follow-up of patients who are not deemed to need surgical treatment after initial assessment, and (6) the post-operative follow-up of patients who undergo surgical treatment. The evidence calls for clinicians to bear in mind the Hippocratian advice "ωφελέειν ή μη βλάπτειν" ("first do no harm").

Contents

Abbreviations: CT, computed tomography; HU, Hounsfield units, MRI magnetic resonance imaging; 18F-FDG, 18fluoro-fludeoxyglucose; PET, positron emission tomography; ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrostenedione-sulfate; Δ_4-A, Δ_4-androstenedione; UFC, urinary free cortisol; FNA, fine needle aspiration.

* Corresponding author at: Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital, Ring Road, Nea Efkarpia, Thessaloniki 56403, Greece.
E-mail address: dimitrios.goulis@otenet.gr (D.G. Goulis).

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1. Introduction

Adrenal incidentalomas are unsuspected lesions that are detected in adrenal glands incidentally during thoracic or abdominal imaging for other causes [1,2]. The reported prevalence of these entities varies. Given the widespread use of imaging – both computed tomography (CT) and magnetic resonance imaging (MRI) – adrenal incidentalomas constitute a common clinical problem [2–6]. Any physician facing an adrenal incidentaloma has to determine two main issues: first, whether the lesion is malignant or benign; and, second, whether it is hormonally active or non-functioning. In order to reach definite answers, proper imaging and functional endocrine tests should be performed. The answers to these questions will guide the treatment strategy, which can vary from follow-up to surgical resection.

Although many original papers and guidelines on adrenal incidentalomas have been published [3,7–13], the optimal diagnostic and therapeutic procedures are still not clear. The objective of this comprehensive review is to discuss updated information on the definition, prevalence, imaging and functional features of various categories of adrenal incidentalomas and to provide a guide for the optimal diagnostic, treatment and follow-up strategy, key aspects of both effective and efficient patient management.

2. Methods

In order to identify publications on adrenal incidentalomas, a literature search was conducted in three electronic databases, PubMed, Cochrane and EMBASE. In addition, a manual search of key journals and abstracts from the major annual meetings in the field of endocrinology was conducted. Special attention was paid to guidelines, as well as to the studies that these guidelines are based on. This review collected, analyzed and then qualitatively re-synthesized information regarding: (1) the clinical entities known as "adrenal incidentalomas", (2) the initial assessment of risk of malignancy, (3) the initial assessment of whether the lesions are hormonally active or non-functioning, (4) the absolute and relative indications for surgical treatment, (5) the follow-up of patients who are not deemed to need surgical intervention after initial assessment, and (6) the post-operative follow-up of patients who undergo surgical treatment.

3. Results and discussion

3.1. Definition and categories of adrenal incidentalomas

The term "adrenal incidentalomas" refers to adrenal lesions that are asymptomatic and detected during imaging for causes other than adrenal pathology. The strict definition excludes lesions <1 cm or masses that are discovered during the staging of an already known tumor [12,13]. Adrenal incidentalomas have been described in both autopsy and imaging studies. The prevalence varies from 1–9% in autopsy studies [1,14,15] to 3–5% in imaging studies [2,5,8,16]. Both types of study have found a positive association with age, with adrenal incidentalomas being extremely rare in childhood and exceeding a prevalence of 10% in people more than 70 years old [1,2,5,8,14–16].

Adrenal incidentalomas can be benign or malignant, and can derive from adrenal cortex or adrenal medulla, or be extra-adrenal in origin (non-functioning adenoma, functioning adenoma, adrenocortical carcinoma, pheochromocytoma, cyst, lymphoma, myelolipoma, ganglioneuroma, metastases). The vast majority of adrenal incidentalomas are benign adrenocortical adenomas (~80%). Most of them are non-functioning (~75%) [1,2,8,13] (Table 1).

Adrenal incidentalomas are most commonly unilateral. Nevertheless, bilateral adrenal incidentalomas are reported in 7.8–15% of cases [2,6,12,17,18]. Most of them are discrete bilateral lesions, while a small percentage appear as diffuse adrenal hyperplasia or enlargement (macronodular or micronodular). The majority of lesions are benign and non-functional. However, the risk of congenital adrenal hyperplasia, metastases, hemorrhage, pheochromocytoma, lymphoma, infectious (such as tuberculosis) or metabolic storage diseases (such as amyloidosis) is higher than with unilateral lesions and should be considered [2,6,12,13,17,18]. There is increasing evidence of differences in both pathophysiology and clinical presentation between unilateral and bilateral adrenal adenomas [19–22]. In accordance with the recent European Society of Endocrinology (ESE)/European Neuroendocrine Association (ENEA) guidelines [13], we would recommend that each lesion be assessed using the same protocol as for unilateral masses.

3.2. Assessment of malignancy

The majority of adrenal incidentalomas are benign. However, the most important question to be answered at the initial assessment of a patient with an adrenal incidentaloma is the possibility of malignancy. The essential tool for this assessment is adrenal imaging. The diagnostic technique of choice is the adrenal CT [13,23]. At first, a non-contrast CT scan will give information about the size and lipid content of the lesion, as well as the smoothness of contour, the homogeneity and vascularity, the presence of lymph nodes and the possible invasion or mass extension to adjacent tissues. The risk of malignancy increases in parallel with mass diameter (≤4 cm: 2%, 4.1–6 cm: 6%, >6 cm: 25%), and decreases with greater lipid content. A threshold of <10 Hounsfield units (HU) is indicative of high lipid content. Sensitivity of HU >10 for the diagnosis of malignancy is 100% and specificity 72% in patients without a history of extra-adrenal cancer [23–25]. Intravenous contrast-enhanced CT can further help. High contrast washout, defined as >60% absolute $[100 \times (HU_{60s} - HU_{15min})/(HU_{60s} - HU_{0s}]$ or >40% relative $[100 \times (HU_{60s} - HU_{15min})/HU_{60s})$, at 15 min is indicative of the benign nature of an incidentaloma [13,23,26,27] (Fig. 1).

If the contrast washout is not high, MRI chemical shift analysis can further help in the diagnostic procedure. Signal intensity loss in out-of-phase images is indicative of lipid-rich content and, therefore, of benign adenomas. Otherwise, the risk of malignancy is high. The use of MRI rather than CT is generally indicated for children, adolescents, pregnant women and young adults (under 40 years old). The likelihood of malignancy in these groups is high [13,23,27,28]. Finally, 18-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET) has high sensitivity for malignancy, but is not specific and should be used only in special cases. It