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Review

Prevalence, Diagnosis and Management of Adrenal Incidentalomas

Meshari Alturki [1], Mommen Naem [2], Ibrahim Al Zehefa [3], Ali Alaeq [4], Mohammed Al-Amri [3], Adam Al Amer [5], Fatema AlDabbous [6], Abdulaali Albogmi [7], Abdullah Al Ghamdi [8], Najla Alomani [9], Kawthar Alqallaf [10]

[1] *Department of General Surgery, Al Thager Hospital, Jeddah, Saudi Arabia*
[2] *College of Agriculture and Veterinary Medicine, Qassim University, Riyadh, Saudi Arabia*
[3] *College of Medicine, King Khalid University, Abha, Saudi Arabia*
[4] *College of Medicine, University of Glasgow, Glasgow, Scotland*
[5] *ICU, Prince Saud Bin Jalawi Hospital, Ahsa, Saudi Arabia*
[6] *Aladan Hospital, Ministry of Health, Fahaheel, Kuwait*
[7] *General Physician, Second Health Cluster Central Region, Riyadh, Saudi Arabia*
[8] *Lab Specialist, Blood Bank Department, Prince Meshary Hospital, Al Baha, Saudi Arabia*
[9] *Department of Radiology, Government Hospitals/SMC, Manama, Bahrain*
[10] *College of Medicine, Mansoura University, Mansoura, Egypt*

Correspondence should be addressed to **Meshari Alturki**, Department of General Suergery, Al Thager Hospital, Jeddah, Saudi Arabia. Email: mtalturki@moh.gov.sa

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Abstract

Adrenal incidentalomas (AIs) are defined as adrenal masses incidentally discovered on imaging studies performed for unrelated reasons. AIs have become a common finding in clinical practice, particularly with the widespread application of high-resolution imaging techniques. While most AIs are non-functioning and benign, some cases can represent a clinical concern due to the risk of malignancy or hormone hyperfunction. The prevalence of AIs varies depending on the source of data and patient selection. The diagnosis of AIs relies on a combination of radiological, biochemical, and clinical evaluation to determine the functional status of the tumor and the potential for malignancy. The management of AIs remains a subject of controversy, with guidelines providing conflicting recommendations on the indications for surgical intervention and follow-up. Most AIs do not require surgical intervention, but appropriate follow-up is essential to detect any potential growth or functional changes. In cases where surgery is indicated, laparoscopic adrenalectomy is the gold standard, with open adrenalectomy reserved for masses highly suspicious for adrenal cortical carcinoma. A multidisciplinary approach involving endocrinologists, radiologists, and surgeons is crucial for optimal management of AIs.

Keywords: adrenal mass, diagnosis, imaging, management

Introduction

Adrenal incidentaloma (AI) is a neoplasm measuring >=1 cm that is incidentally discovered during a procedure performed for other causes than suspected adrenal disease or secretion (1). The detection of AIs has increased in recent years, because of the large availability of medical imaging equipment such as computed tomography (CT, 41 units per 1 million population in the United States, US) and magnetic resonance (MR, 38 units per 1 million population in the US). The utilization of diagnostic imaging has experienced a significant surge in the past 30 years due to various factors, such as the advancement of imaging technologies, greater emphasis on preventive healthcare, the proliferation of diagnostic imaging facilities, and the rising incidence of chronic illnesses linked to the aging of the population (2).

The prevalence of AIs varies according to the age of patients and the method of detection. Autopsy data suggest that less than 1% of AIs are found in young people and the prevalence increases up to 15% in people over 70 years old. On the other hand, in radiological studies, the peak incidence is reached in the fifth to seventh decades of life, with the frequency of AIs being around 4% in middle-aged adults and up to 10% in the elderly (3). The incidence of adrenal tumors is nearly equal in men (45%) and women (55%). Adrenal tumors are a rare occurrence in children, with only 1% of all cases being diagnosed in patients under 18 years old (4). While most AIs are unilateral tumors, bilateral AIs are present in as many as 15% of cases, indicating that the prevalence of bilateral AI in the general population can be estimated to be 0.3-0.6% (5).

Adrenal tumors can be categorized into five major groups: adrenal adenomas and nodular hyperplasia; non-cancerous lesions such as myelolipomas, cysts, hematomas; adrenocortical carcinomas; other malignant tumors including metastases, sarcomas, lymphoma; and pheochromocytomas. Adrenal incidentalomas are usually non-hypersecreting adrenocortical adenomas; however, they can also indicate primary or metastatic malignancies with minor endocrine abnormalities or subclinical hyperfunction (3). Adrenal medullary tumors, mainly pheochromocytomas, are less frequent. Corticomedullary tumors, which are a combination of cortical and medullary tumors, are also occasionally found (6).

The primary goals of the initial evaluation of AI are to rule out the possibility of malignancy by utilizing clinical data and imaging techniques and to determine the functionality of the lesion through analysis of clinical history and biochemical-hormonal studies (7). Clinical history should be obtained to exclude symptoms and signs suggesting malignancy and endocrine activity of incidentaloma and assess comorbidities (8). Precise radiologic assessment is a part of primary evaluation and normally involves computed tomography-CT with/without contrast and Magnetic resonance imaging (MRI) (9).

The aim of the endocrine assessment is to determine which patients are suitable for surgery. This assessment should comprise a fundamental biochemical analysis as well as a screening test for hypercortisolism and pheochromocytoma in all patients. Moreover, in patients with hypertension and/or hypopotassemia, a screening test for primary hyperaldosteronism should be conducted (10). If a hormonally inactive mass is indeterminate on imaging and the histology results would affect the patient's management, a fine-needle aspiration biopsy can be considered in a multidisciplinary approach (7). As the majority of AIs are benign and non-functioning, surgical treatment is not routinely required (7). Surgical intervention is the preferred treatment for functioning AI, which present with overt hormonal syndromes, and in cases where there is a suspicion or confirmed diagnosis of malignancy. A multidisciplinary team should evaluate the need for surgery in certain special situations such as an indeterminate adrenal mass over 4-6 cm in size, lesions with atypical features on imaging, or those that demonstrate changes in radiological characteristics or growth during follow-up (defined as a 20% increase in the major diameter or an absolute increase of over 5 mm in the major diameter) (11).

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In this literature review we aim to summarize the current understanding of prevalence, diagnosis and management approaches of adrenal incidentalomas.

Methodology

This study is based on a comprehensive literature search conducted on April 12, 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. Articles published in the period between 2000 and 2023 were mostly included. To avoid missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about prevalence, diagnosis and management of adrenal incidentalomas. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Prevalence

The detection of adrenal masses without any clinical symptoms during imaging studies, known as adrenal incidentalomas, has become a frequent occurrence in clinical practice. These masses are usually benign and non-hypersecreting, but the potential for malignancy or hormone hyperfunction still poses a significant concern. As knowledge of the imaging and hormonal evaluation of adrenal incidentalomas continues to expand, there is a growing understanding of their epidemiology and natural progression (10).

The incidence of adrenal incidentalomas varies based on the type of data source (e.g., autopsy or radiological studies) and patient selection (e.g., general population or specific patient groups) (4). The increasing availability of high-resolution imaging technology has led to a significant rise in incidentally discovered adrenal masses, which has become a prevalent issue, particularly among the aging population (3).

The reported prevalence of AI in autopsy series with large patient numbers (series with greater than 1000 patients) ranges from 1.05% to 8.7% (3). Kobayashi et al. conducted a large retrospective study in Japan where they analyzed primary adrenocortical tumors recorded in the Pathological Autopsy Case Annuals between 1973 and 1984. The study, which included 321,847 cases, reported a significantly lower overall prevalence of 0.03% of adrenocortical adenomas compared to historical series. However, the prevalence of adenomas increased with age, with the highest prevalence observed in the fifth and sixth decades of life. Of the adenomas identified in the study (n = 101), only 25 were found in patients younger than 50 years, while the remaining 75% were found in patients over 50 years old (12). The variability in reported prevalence among postmortem series is considered to be due to differences in patient selection, inclusion criteria, and the challenge of differentiating nodular hyperplasia and small adrenal nodules or adenomas (4).

The prevalence of AIs reported in the first CT scan series between 1982 and 1986 was underestimated at 0.6% to 1.3% due to low-resolution technology and the failure to detect smaller lesions (13). However, contemporary high-resolution CT techniques report a prevalence closer to that observed at autopsy. Similarly, Song et al. reported a prevalence of 5% for AI in a retrospective study of CT reports, which could be due to dedicated radiological review of adrenal imaging in a significant percentage of cases, resulting in the diagnosis of more AI than in routine radiological clinical practice (14).

Adrenal incidentalomas are commonly diagnosed in clinical reports, particularly in patients in their fifth to seventh decades, with a mean age of diagnosis at 55 years and no significant difference between genders. The female to male ratio is reported to be 1.3-1.5 (3). Although there is no sex bias reported in autopsy studies, the higher prevalence of adrenal incidentalomas in females is likely due to the increased frequency of abdominal diagnostic procedures performed in women compared to men. Adrenal masses are distributed asymmetrically with the right adrenal gland affected in 50-60% of cases, the left adrenal gland affected in 30-40% of cases,

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and bilaterally affected in 10-15% of cases (15). This difference in distribution can be attributed to the lower efficiency of ultrasonography in detecting tumors on the left side. Similar distribution between the two adrenal glands has been reported in CT scan and autopsy series (3).

Adrenocortical adenomas that are non-hypersecreting are the most common cause of adrenal incidentalomas. However, there are cases where the masses can be primary or metastatic malignancies or show minor endocrine abnormalities or subclinical hyperfunction (3). Recent systematic review by Sconfienza et al. focused on the prevalence of functioning incidentalomas. The prevalence of functioning AIs was determined to be 27.5%. Among the hormonal alterations observed, autonomous/possible autonomous cortisol secretion (ACS) had the highest prevalence at 11.7%, followed by primary aldosteronism (PA) at 4.4%. The prevalence of PA was higher in patients from Asia compared to those from Europe/America, whereas ACS/possible ACS had a lower prevalence in Asian countries. The proportion of female patients influenced the prevalence of ACS/possible ACS, while the prevalence of PA was positively associated with the proportion of patients with hypertension and the publication year. Additionally, the prevalence of pheochromocytoma and Cushing syndrome were 3.8% and 3.1%, respectively (10).

Overall, prevalence and epidemiological characteristics of AIs still remain unclear. There is a need for large-scale comprehensive research to assess modern scientific evidence on the issue.

Diagnosis

The diagnostic approach to AIs focuses on three main aspects: assessment of hormonal function, imaging evaluation, and risk stratification for malignancy. Clinical evaluation of patients with AIs includes a thorough medical history, physical examination, biochemical testing, and imaging studies (9).

When assessing adrenal masses, it is crucial to determine the functional status of the tumor, identify any malignancy, and ascertain whether the patient reports any associated symptoms. Although most adrenal masses are nonfunctional, comprising approximately 80% in some series, there is still a real risk of functional adenomas (5%), pheochromocytomas (5%), adrenocortical carcinomas (16) (<4%), and metastatic lesions (<2%) (17). Therefore, a thorough history and physical examination should be conducted to rule out or diagnose a functional tumor. When reviewing the patient's symptoms, physicians should particularly highlight symptoms suggesting endocrine disturbances, including headaches, flushing, palpitations/arrhythmias, tremor, anxiety, easy bruising or bleeding, insomnia, fatigue, weakness, muscle cramping, poor wound healing, sudden changes in weight, hair loss, and easy tearing of skin/thinning of skin. Medical history of current medication use, and family history of adrenal or other endocrine disorders and cardiovascular disease should also be obtained. It is important to inquire about age-appropriate cancer screening and any personal risk factors for malignancy (8).

A complete physical examination should be conducted with attention paid to heart rate and blood pressure, looking for tachycardia and/or hypertension. Additional physical findings to note include moon facies, buffalo hump, increased supraclavicular fat pads, striae, central obesity with peripheral wasting, cardiac arrhythmias, tremor, ecchymosis of extensor surfaces of upper extremities, thinning of skin or hair, and/or agitation (4). Biochemical testing is an important component of the diagnostic evaluation of AI. Hormonal hypersecretion, although uncommon in AI, can be associated with significant morbidity and mortality. Screening for hormonal hypersecretion includes measurement of plasma or urinary metanephrines and catecholamines for pheochromocytomas, plasma aldosterone and renin activity for primary aldosteronism, and overnight dexamethasone suppression test for cortisol-secreting adenomas. In cases where biochemical testing suggests hormonal hypersecretion, additional confirmatory testing such as clonidine suppression test or saline infusion test may be necessary (1, 18).

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Imaging evaluation is necessary to characterize the lesion and assess for features suggestive of malignancy: size, morphology, and radiological characteristics of the mass (18). There are different imaging modalities that can be used for the evaluation of AIs, including computed tomography (6), magnetic resonance imaging (MRI), and positron emission tomography scan (4) (4, 19). CT is the most commonly used imaging technique due to its high sensitivity and specificity in detecting adrenal masses. However, MRI may be preferred in certain situations, such as for patients with renal insufficiency or iodine allergy (8). PET scan may be useful for the evaluation of suspected malignancy, particularly in cases where CT and MRI are inconclusive (20).

Risk stratification for malignancy is an essential aspect of the diagnostic approach to AIs. The risk of malignancy increases with larger size of the lesion, presence of irregular margins, heterogeneous enhancement, and imaging features suggestive of invasion into surrounding structures (13). The use of adrenal biopsy in clinical practice remains a subject of debate. A fine-needle aspiration biopsy may be deemed appropriate in a collaborative setting provided that the mass is confirmed as hormonally inactive, the imaging results are inconclusive, and the histological results would significantly affect the patient's management (1).

There are five categories of adrenal incidentalomas according to histopathology findings, including adrenal adenomas and nodular hyperplasia, non-cancerous lesions such as myelolipomas, cysts, and hematomas, adrenocortical carcinomas, other malignant tumors such as metastases, sarcomas, and lymphoma, and pheochromocytomas. Adrenal incidentalomas, which are commonly non-hypersecreting adrenocortical adenomas, may also indicate primary or metastatic malignancies that cause minor endocrine abnormalities or subclinical hyperfunction (1).

Accurate diagnosis and characterization of AIs is crucial to guide appropriate management. A multidisciplinary approach involving endocrinologists, radiologists, and surgeons is recommended to ensure a comprehensive evaluation and individualized management plan for patients with AIs.

Management

The majority of AIs are typically benign and non-functional, hence surgery is generally unnecessary. However, the challenge arises when determining the need for follow-up and how it should be performed (13). The absence of a consensus among various guidelines regarding the indications and duration of follow-up exacerbates this dilemma. This lack of consensus is primarily due to the scarcity of solid scientific evidence, as most existing studies are retrospective with limited case series or prospective studies with short follow-up periods. Additionally, the prevalence and incidence of adrenal carcinoma are very low, making it challenging to estimate the malignancy risk of AIs during the follow-up period (7).

Patients with functional unilateral adrenal masses that do not have radiological features concerning for malignancy should be referred for laparoscopic adrenalectomy, while appropriate perioperative management is essential to ensure patient safety (8). Adrenal masses highly suspicious for adrenocortical carcinoma (16) should be referred for open adrenalectomy. In the case of unilateral adrenal masses with indeterminate imaging findings or size larger than 4 cm, surgical intervention should be offered. The surgical approach for these may be either laparoscopic or open, depending on individual patient factors (11). Unilateral adrenal myelolipomas are diagnosed based on imaging characteristics alone, due to the presence of large amounts of fat in the adrenal mass. These masses do not generally require surgical intervention. However, surgery may be considered if the myelolipoma is causing symptoms of mass effect or rapid growth is noted (9).

Laparoscopic adrenalectomy is considered the gold standard for most adrenal masses. This approach has been shown to have the least postoperative pain, shorter hospital stays, and decreased blood loss, as well as faster recovery time (11). Patients should ideally be referred to a high-volume adrenal surgeon

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(performing more than four adrenalectomies per year) for optimal clinical outcomes. Patients with known or suspected ACC should be considered for open adrenalectomy due to the high risk of local recurrence and peritoneal carcinomatosis (1). It is recommended to administer perioperative glucocorticoid treatment at major surgical stress doses, in accordance with guidelines, for all patients who undergo surgery for an adrenal tumor and show evidence of "possible autonomous cortisol secretion"(1).

Conclusion

Adrenal incidentalomas are common and increasingly detected through high-resolution imaging. While most are benign, some may be functional tumors requiring a comprehensive diagnostic approach. Surgery may be necessary for functional or suspicious masses, but the management of non-functioning masses is uncertain and should be individualized based on clinical presentation, imaging findings, and risk factors. Further research is needed to optimize management strategies for these common clinical entities.

Disclosure

Conflict of interest

There is no conflict of interest

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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