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INVESTIGATION OF THE CLINICALLY INAPPARENT ADRENAL MASS (INCIDENTALOMA)

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ABSTRACT
An adrenal incidentaloma is an adrenal mass (≥1 cm in diameter) mainly detected unexpectedly, by an imaging study performed for reasons unrelated to any suspect of adrenal diseases, which may be in one or both adrenal glands. It is estimated that adrenal masses under 1 cm do not need additional diagnostic examinations, except in cases where there are clinical or laboratory suspicions of adrenal hormonal overproduction, or there are features that raise concern regarding malignancy. The differential diagnosis of adrenal masses consists of distinguishing between a benign, non-functioning adenoma or adrenocortical carcinoma. Adrenal incidentalomas are increasingly recognized in medical practice, making this a medical challenge. Although adrenal incidentaloma is a common endocrine diagnosis, it requires a multidisciplinary expert team for effective management. There is still ambiguity in the current guidelines regarding the management of small indeterminate incidentalomas, which constitutes a problem in terms of clinical solutions in real practice.The majority of patients with adrenal incidentalomas still do not undergo the recommended hormonal workup. The aim of this article is to review of the proposed strategies regarding the investigation and management of adrenal incidentalomas, collating recommendations from international guidelines.

KEYWORDS: Adrenal mass, non-functioning, incidentaloma.

INTRODUCTION
An adrenal incidentaloma is an adrenal mass (≥1 cm in diameter) mainly detected unexpectedly by an imaging study performed for reasons unrelated to any suspect of adrenal diseases.[1] The etiology of adrenal incidentalomas includes benign and malignant masses derived from the adrenal cortex or medulla or masses of extra-adrenal origin. There is a large differential diagnosis for these masses; ranging fromadenomas 41%, 19% metastases, 10% adrenocortical carcinomas, 9% myelolipomas, around 7% phaeochromocytomas, and the remainder are mostly benign tumours (cysts, adrenolipomas, haematomas, leiomyomas, and lymphangiomas). Most hormonally active adrenal tumours causing Cushing's syndrome, phaeochromocytoma, or primary hyperaldosteronism are benign, but uncommonly they may be malignant. Adrenocortical carcinoma is a rare tumor, but is frequently hormonally active.[2,3] When an adrenal mass is incidentally identified, the key clinical questions are whether it is functioning and whether it is malignant, which may require a multidisciplinary involvement for the approriate management.[1]

Prevalence and etiology of adrenal incidentalomas
The incidence and prevalence of adrenal masses varies depending on the source of data: unselected imaging or autopsy studies. Autopsy studies suggest an overall prevalence of adrenal masses of around 2% (range 1.0%-8.7%). The prevalence of adrenal incidentaloma in the general population is evaluated 1% to 6%,[4] which increases with the wide use of new diagnostic procedures for further exploration, and with aging of the population.Adrenal tumors in children are very rare and mostly not incidentaloma.[5] The prevalence is higher among older adults~3% of those aged over 50 years with a peak ≤7% in those aged over 70 years.[1] In a population study in japon from 1999 to 2004, in which 3672 cases were included with clinically diagnosed adrenal incidentaloma, 1874 men and 1738 women, with an average age 58.1 ± 13.0 years, from the endocrinological evaluations resulted that 50.8% of total AIs were non-functioning adenomas, while 10.5%, including 3.6% with subclinical Cushing's syndrome, were reported as cortisol-producing adenomas, 8.5% as pheochromocytomas, and 5.1% as aldosterone-producing adenomas. Adrenocortical carcinoma was accounted overall 1.4%. By the radiological evaluation compared to non-functioning adenomas, tumor diameters are larger in adrenocortical carcinomas, pheochromocytomas, cortisol-producing adenomas, myelolipomas, metastatic tumors, cysts, and ganglioneuromas.[6] From the imaging data of the NHS diagnostic imaging dataset (6 million CT and 3.8 million MRI scans) of 2018, it resulted that

majority of adrenal incidentalomas are benign, but ∼2% represent primary adrenal malignancies, and∼14% of adrenal incidentalomas are functional tumours that may secrete excess cortisol, aldosterone, catecholamines or (rarely) androgens.[7]

The etiology of adrenal incidentalomas varies and includes benign and malignant lesions derived from the adrenal cortex or medulla or masses of extra-adrenal origin. Classification of adrenal incidentaloma based on structural appearances, is categorized in five groups:

- Adrenal adenomas and nodular hyperplasia;
- Other benign lesions (myelolipomas, cysts, haematomas, etc);
- Adrenocortical carcinomas (ACC);
- Other malignant tumours (metastases, sarcomas, lymphoma etc) (adrenal cancers ∼4%);
- Phaeochromocytomas (∼7%).

Assessment for hormone excess

Endocrinologists recommend a clinical examination for signs of adrenal hormone excess and biochemical testing in every patient with adrenal incidentaloma to detect pheochromocytoma, excess cortisol secretion, and those who also have high blood pressure should undergo biochemical testing to detect primary hyperaldosteronism.[8]

Catecholamine excess (phaeochromocytomas)

On careful history and physical examination, many patients are found to have classic symptoms or signs of pheochromocytoma (headache, palpitations and profuse sweating with signs of resistant or paroxysmal hypertension), a family history of these masses, or both.[9] The most used screening tests to detect pheochromocytoma are measurement of the levels of plasma-free metanephrines (sensitivity, 89 to 100%, and specificity, 79 to 98%) or 24-hour urinary fractionated metanephrine level (sensitivity, 86 to 97%, and specificity, 69 to 95%), although both false-positive and false-negative results may arise.[10] The next step in evaluation after biochemical tests suggest pheochromocytoma is to locate the tumor. Imaging tests, especially CT or MRI, help localize tumors. CT is suggested for initial imaging, with MRI in metastatic disease patients or to limit radiation exposure.Imaging features on CT (attenuation of more than 10 Hounsfield units on unenhanced CT, the presence of areas of increased vascularity and necrosis on enhanced CT, and delayed washout of contrast medium), may be helpful in suggesting pheochromocytoma.[9] For metastatic disease, 18F-FDG PET scanning and 123I-MIBG scan are recommended. All patients diagnosed with pheochromocytoma should be considered for genetic testing.[11]

Glucocorticoid excess (Mild hypercortisolism)

To diagnose the etiology of adrenal incidentalomas, ESE/ENSAT guidelines recommend that all patients should undergo a 1 mg overnight dexamethasone suppression test to exclude cortisol excess. Cortisol concentration ≤ 50 nmol/L post dexamethasone may be regarded as physiologic, excluding cortisol excess, whilecortisol concentrations between 51–138 nmol/L (without clinical signs of overt Cushing's syndrome) indicate possible mild autonomous cortisol secretion (MACS) and >138 nmol/L indicates MACS in the absence of clinical features of Cushing's syndrome. The patients who suppress cortisol below 50 nmol/L do not need any further evaluation or follow-up by an endocrinologist.[8] MACS is the most common hormonal abnormality diagnosed in 18.9% to 45.3% of patients with adrenal mass.[12] Adrenocorticotropine quantification after dexamethasone suppression test, may be necessary to verify the independence of Cushing syndrome from ACTH secretion. MACS is associated with comorbidities attributable to cortisol like diabetes mellitus, hypertension, obesity, dyslipidemia, or osteoporosis and with an increased risk of cardiovascular events and excess mortality.[12,13] Two recent cohort studieshave noticed that morning cortisol > 80 nmol/L after 1 mg dexamethasone is associated with increased all-cause mortality in patientswith adrenal incidentaloma and possible MACS,[14,15] and morning cortisol of >50 nmol/L after 1 mg dexamethasone has highest sensitivity and specificity to predict cardiovascular events.[16] It is evident that 'autonomous cortisol secretion' is not a condition associated with a high risk to develop overt Cushing syndrome. The most important consideration is to treat cardiovascular risk factors and co-morbidities in these patients.

Mineralocorticoid excess

Primary hyperaldosteronism (PA) an underdiagnosed cause of hypertension, is the most common specifically treatable and potentially curable form of hypertension, caused by aldosterone-producing adenomas, aldosterone-producing adrenal carcinoma, ectopic aldosterone secretion from the kidneys or ovaries, and bilateral adrenal hyperplasia of the zona glomerulosa. Familiar cases of hyperaldosteronism are classified in: Type I (is glucocorticoid-remediable hyperaldosteronis that results from the formation of a chimeric gene containing the regulator portion of 11B-hydroxylase), Type II (correlates to a gene on 7p22 with histologic findings consistent to hyperplasia or adenomas, and Type III (results from a mutation in KCNJF, which is a potassium channel coding gene).[17] A young patient withuncontrolled hypertension and hypokalemia must be checked for primary hyperaldosteronism, however, estimates are now that less than 37% of patients who have primary hyperaldosteronism will present with hypokalemia.[18] There are no physical exam characteristics that will lead to a diagnosis of primary hyperaldosteronism, but findings related to longstanding hypertension like heart failure, proteinuria, hypertensive retinal changes, carotid bruits/stroke symptoms, muscle weakness, and mental status changes secondary to hypertensive encephalopathy may be present. The Endocrine Society recommends screening for PA

patients with hypertension on triple-drug therapy and diuretic-induced hypokalemia; patients with hypertension and adrenal incidentaloma; hypertension with a family history of the early-onset cerebral vascular accident; or patients with hypertension and first-degree relatives with confirmed primary hyperaldosteronism.[19] PA should be screened for by measuring the aldosterone/ renin ratio (ARR), and if the ratio of morning aldosterone to plasma renin activity is higher than 20 to 1, then the excess aldosterone can be attributed to the adrenal gland as the primary source. Any of the four confirmatory tests may follow: 1) saline infusion, 2) oral sodium loading 3) fludrocortisone suppression 4) captopril challenge, which should suppress aldosterone. In a patient with primary aldosteronism, there will be a lack of aldosterone suppression.[17,18] All patients that PA is confirmed are recommended to undergo an adrenal computed tomography scan as the initial study and to exclude adrenocortical carcinoma.It is also recommended for the patient to have an adrenal venous sampling as the best diagnostic test, which involves the measurement of cortisol and aldosterone in bilateral adrenal venous effluent and a peripheral vein before and during an ACTH infusion. When an adenoma is present, the aldosterone-to-cortisol ratio on one side is usually at least five times greater than the other, indicating suppression, while bilateral hyperplasia tends to produce similar values on each side.[20] Laparoscopic adrenalectomy is the preferred treatment for unilateral adenoma, while if the patient declines surgery or is not a surgical candidate (bilateral hyperplasia), medical treatment with a mineralocorticoid antagonist is the recommended route.[18,19,20]

Steroid profiling

Several studies have evaluated the importance of the steroid profile to differentiate benign from malignant lesions.[21] Only 2 studies focused on incidentalomas reported diagnostic accuracy measures for steroid profiles, to assess the risk of malignancy. One large prospective study (n=2017) employed urine steroid metabolomics,[22] while one retrospective study (n = 577) used plasma steroid profiling,[21] which concluded that the sensitivity for both urine and plasma steroid profiling as a stand-alone test has not high sensitivity (about 80%) approaches to rule out malignancy with certainty. Urine steroid profile when combined with imaging criteria (size > 4 cm and HU >20) has higher diagnostic accuracy for malignancy than imaging alone.[23]

Radiological evaluation of adrenal lesions

The role of radiology plays in identifying and assessing adrenal lesions.[24] Abdominal ultrasound usually performed as screening examination in patients with abdominal discomfort or nonspecific abdominal pain, has a significantly lower detection rate compared with CT and magnetic resonance (MRI) in the identification of lesions smaller than 3 cm. Abdominal ultrasoundcannot correctly distinguish between benign and malignant nodules, but on the contrary is a reliable tool in lesion staging.[25] Unenhanced CT is commonly the first imaging modality identifying adrenal lesions, which allows for precise lesion measurement and accurate density evaluation. Similar to CT, the results of MRI with chemical shift imaging are based on the lipid content of masses, which has the advantage of avoiding ionizing radiation and its attendant risks to the patient. The meta-analysis was not able to determine the diagnostic value of MRI, especially compared to CT, due to the low number and quality of studies.[26] Currently, CT scan and MRI are the imaging modalities of choice with the highest diagnostic accuracy regarding the detection of the nature of the lesion and the presence of malignant potential.

CT scan

The best way to distinguish between benign and malignant tumors is based in the non-contrast CT attenuation coefficient, expressed in HU. The diagnostic criteria for benign adenoma used in the past studies is an attenuation coefficient of ≤10 HU in a non-contrast CT, and the specificity of this criterion was 71% to 79% with a sensitivity of 96% to 98%.[27] However, 10% to 40% as 30% of adenomas are lipid-poor and thus show an HU value >10, further assessment may be necessary.[28] Important criterion to distinguish benign from malignant lesions are the size of the lesion and pattern after contrast enhancement. Other signs that suggest malignancy are size greater than 4 to 6 cm on a CT scan, a tumor with an irregular margin or heterogenecity, an attenuation coefficient more than 10 HU in a non-contrast CT, washout of the contrast agent after 10 or 15 minutes of less than 40%, calcification, and invasion into surrounding tissue.[29]

MRI

Various studies found no significant advantage for MRI over a CT scan in distinction adenomas from non-adenomas. In addition, the meta-analysis was not able to determine the diagnostic value of MRI, especially compared to CT, due to the low number and quality of eligible studies.[30] The advantages of MRI over CT are avoiding ionizing radiation and its attendant risks to the patient. The best MR imaging technique to characterize suprarenal adenoma is found to be chemical shift imaging (CSI), with findings such as reduced T1 signal and increased T2 signal suggestive of malignancy or pheochromocytoma.[31] The results of MRI with chemical shift imaging are based on the lipid content of masse, similar this to CT. Its sensitivity and specificity in diagnosis of indeterminate adrenal lesions are reported as 67% and 89–100%, respectively.[32] MRI with chemical shift would be first choice only where a CT is less desirable, like in children or pregnancy.

Molecular Imaging

Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET has a high sensitivity for detecting hypermetabolic metastatic lesions and is particularly useful to exclude extra-adrenal disease, as malignant lesions have increased metabolic

activity and, therefore, increased glucose avidity compared with benign lesions, with a sensitivity between 93% and 100%.[33] It is recognized that FDG-PET has a low sensitivity and specificity for characterizing adrenal lesions <10 mm.[34] FDG, 18-F-dihydroxylphenylaalanine (DOPA), Ga-68-DOTATATE, or I-123 metaiodo benzylguanidine (MIBG) are used for diagnosis and staging of phaeochromocytomas.[35]

CONCLUSION

Adrenal incidentalomas being a common finding, it is important to make an accurate clinical, laboratory and imaging evaluation to determine their functional status and the risk of malignancy. The multidimensional team plays an important role about the managerial decision-making for the indefinite masses.

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