Endocrinology

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Adrenal incidentalomas: 'the rule of four'

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The widespread use of abdominal imaging, particularly computed tomography (CT) and magnetic resonance imaging (MRI), during diagnostic testing or treatment for many clinical conditions has resulted in the inadvertent discovery of adrenal masses when no adrenal disease is suspected by the clinical presentation. These masses, first defined 25 years ago, are termed 'adrenal incidentalomas'.[1]

The adrenal incidentaloma is not a single pathological entity. Its management is influenced by the interpretation of clinical, biochemical and imaging data in order to assess the functional status, the potential malignancy and the long-term sequelae that may relate to subclinical hormone hypersecretion. Improvements in biochemical and imaging modalities over the past few years increasingly offer significant tools to aid clinical decision making for the most appropriate management of such ill-defined adrenal masses.

Prevalence and aetiology

The prevalence of the adrenal incidentaloma is not known with precision since the published data vary according to the definition of each investigator, the inclusion criteria of the patients studied and the circumstances under which the data of the patients have been collected. Autopsy series report a prevalence of 1.4–2.9% of previously undiagnosed adrenal masses, but with more lax size criteria it may increase to 8.7%.[2–4] The most recent imaging studies which detected smaller-sized lesions report a prevalence of around 4%.[1,3,5–7]

The protean causes of adrenal incidentalomas have been described in several studies. Combining the studies that used the broadest definitions of incidentaloma, a recent review has reported the aetiology of incidentalomas (Table 1).[4] Adenomas comprise the vast majority, their number increasing with age:[4] an incidental adrenal adenoma can be found with a prevalence of 0.2% in an abdominal CT in a patient 20–29 years of age compared with approximately 7% in a patient over 70 years.[5] Even if most adrenocortical masses are non-hypersecretory adenomas, 5–47% secrete cortisol and 1.6–3.8% mineralocorticoids,[2,4–6] while benign masses secreting androgens or oestrogens are extremely rare.[4]

Table 1. Aetiology of adrenal incidentalomas.[4,7]

Aetiology	%
Adenoma	41
Metastases	19
Adrenocortical carcinoma	10
Myelolipoma	9
Phaeochromocytoma	8
Other rare entities*	13

*Mostly benign lesions such as infective diseases (tuberculosis, histoplasmosis), adrenal cysts, adrenal hyperplasia, haematomas, haemangiomas, neurinomas, angiomyelolipomas, ganglioneuromas, angiosarcomas, leiomyosarcomas, malignant epithelial carcinomas, primary lymphomas, neuroblastomas and composite adrenal tumours.[4,7]

Subclinical autonomous glucocorticoid hypersecretion

Most adrenal incidentalomas secreting glucocorticoids do not result in obvious Cushing's syndrome, but many show low-grade autonomous cortisol secretion revealed by abnormal dynamics of the hypothalamic–pituitary–adrenal axis. For this reason, the terms subclinical Cushing's syndrome or subclinical autonomous glucocorticoid hypersecretion (SAGH) have been used.[8,9] There is evidence for an increased prevalence of certain of the problems associated with Cushing's syndrome in patients with SAGH, such as increased cardiovascular risk factors (hypertension, central obesity, diabetes, impaired glucose tolerance, hyperlipoproteinaemia) and an increased risk of osteoporosis, supporting the significance of their early recognition and appropriate management.[10,11]

Mineralocorticoid-secreting tumours

The presence of hypokalaemia (≤3.5 mmol/l) in hypertensive patients with adrenal incidentalomas increases the suspicion of an aldosteronoma. Many patients with hyperaldosteronism and a suppressed plasma renin present with normokalaemia,[4,5,12] but most of these do not harbour a Conn's adenoma, a discrete aldosterone-secreting adenoma. Thus, in this situation the serum potassium remains a helpful pointer.

Phaeochromocytomas

Approximately 4–5% of adrenal incidentalomas have proved to be phaeochromocytomas, even in normotensive patients.[5,13] Phaeochromocytomas are among the most life-threatening endocrine diseases, leading to significant morbidity and mortality even when

apparently clinically silent.[14] The great majority (90%) of phaeochromocytomas are located in the adrenal glands, occurring bilaterally in approximately 10% of patients often in association with familial syndromes.[15,16] These include multiple endocrine neoplasia type 2 (MEN-2), von Hippel-Lindau syndrome, neurofibromatosis type 1 (NF-1), and inherited mutations of the mitochrondrial enzyme succinic dehydrogenase.

Adrenocortical carcinoma

Adrenocortical carcinomas were found in 4.7% of patients in one large series.[13] The size of the mass and its appearance on imaging are considered the major predictors of malignancy. Adrenocortical carcinoma is however rare and usually has a very poor prognosis with overall median survival of 18 months.[4,5,17] Adrenocortical carcinoma can be functional or non-functional with regard to hormone synthesis and clinical features.[17] Hypercortisolism, leading to Cushing's syndrome or a mixed Cushing-virilising syndrome, is present in about 50% of patients; androgen-secreting tumours are more common in children than in adults, while oestrogen-secreting tumours are rare.[4,5]

Metastatic tumour masses

Metastatic cancer was found in 2.5% of adrenal incidentaloma patients in one very large series.[13] Among cancer patients, 50–75% of adrenal incidentalomas are metastases.[2,4,5,13] The most commonly metastasising cancers are carcinomas of the lung, kidney, colon, breast, oesophagus, pancreas, liver, stomach, lymphomas, leukaemia and melanomas.[4,7,18] Metastases to the adrenal glands are frequently bilateral; the primary tumour is usually obvious and interference with adrenal function is uncommon.

Diagnostic work-up

Clinically silent adrenal masses can be functioning or non-functioning, and benign or malignant. A combination of a biochemical and imaging diagnostic work-up is required to enable optimal decision making.

Key Points

- **Incidentally-discovered adrenal masses (incidentalomas) are seen increasingly with the improvements in imaging techniques**
- **The functionality of adrenal incidentalomas can be assessed by simple screening tests including the measurement of serum potassium (possibly renin and aldosterone levels), urinary or plasma catecholamines or their metabolites, and the dexamethasone suppression test**
- **Computed tomography (CT) and magnetic resonance imaging algorithms can be used to identify benign, lipid-rich adenomas in many cases, and therefore provide reassurance**
- **Surgery is recommended for masses of uncertain imaging, for larger masses and for those with significant functional activity**
- **Adrenal adenomas commonly show low-grade hormonal secretion, usually cortisol, but the metabolic implications of this are unclear at present**
- **We suggest that 'the rule of four' is a useful mnemonic for this common problem: an adrenal incidentaloma is found in 4% of CT scans (accepting this as a mean across all ages), some 4% of which are either phaeochromocytomas or adrenocortical cancers, a diameter of 4 cm is used to initiate mandatory removal, and the current recommendation of follow-up is four years**

KEY WORDS: adrenal, Conn's syndrome, Cushing's syndrome, incidentaloma, phaeochromocytoma

Biochemical investigations

Since the long-term sequelae related to subclinical hormone hypersecretion of adrenal incidentalomas are still under investigation, it is important to identify the functional status of an ill-defined mass using simple biochemical tests. The overnight low-dose dexamethasone test can be used to identify hypercortisolism; it involves oral administration of 1 mg dexamethasone at 23.00 hours, followed by measurement of serum cortisol at 08.00–09.00 hours the following morning. Greater sensitivity and specificity are achieved using the standard low-dose dexamethasone suppression test, giving dexamethasone 0.5 mg six-hourly for 48 hours, using a criterion of an 09.00 hours serum cortisol below 50 nmol/l.[19,20]

In order to exclude aldosteronism, it has been recommended that renin and aldosterone levels should be measured. However, as noted above, it is unclear whether this is absolutely essential in the absence of hypokalaemia.[4,5,12,21]

Plasma or urinary catecholamines or fractionated metanephrines should be determined in order to exclude a phaeochromocytoma. There is as yet no consensus as to which test is optimal, but increasing evidence favours measurement of metanephrines rather than catecholamines.[15,16] Sex hormone-secreting adrenocortical tumours typically result in marked clinical manifestations. Screening for excess androgens or oestrogens in patients with adrenal incidentalomas is generally not recommended unless there are relevant clinical features.[5]

Imaging studies

The major contribution of imaging studies in the management of adrenal incidentalomas is to differentiate between benign and malignant lesions, and also to add information about mass functionality.

CT and MRI help identify the possible malignancy of an adrenal mass, based on size and appearance criteria. A cut-off maximum diameter of 4 cm has been found to differentiate benign from malignant lesions with reasonable

accuracy,[4,18] although some would regard all lesions above 3 cm in diameter with suspicion.[4,7] It is important to use a size criterion that allows malignancy to be excluded with high specificity, accepting that many smaller benign lesions will necessarily be selected for removal.[4,22] With increasing size, the probability of malignancy becomes higher; in lesions over 6 cm the ratio of benign-to-malignant tumours is 1:8.[4]

Computed tomography. The major characteristics of CT imaging used to distinguish adenomas from non-adenomas are based on their lipid content.[7,18] Small, solid homogeneous masses with low attenuation values (<10 Hounsfield units (HU)) on unenhanced CT can be considered to be benign lipid-rich adenomas. In the presence of bilateral disease, heterogeneous masses or a mass attenuation above 10 HU, delayed contrast-enhanced CT should be performed at 60 sec and 15 min after intravenous contrast administration. Adenomas typically exhibit rapid washout of contrast medium whereas other adrenal non-adenomas show a more delayed washout.[7,18] The *absolute* contrast washout calculation can differentiate adenomas (>60% contrast washout) from non-adenomas (<60% contrast washout). If the mass is imaged only on post-contrast scans (a frequent situation for the incidentally-discovered adrenal mass), the *relative* contrast washout criteria can be calculated.

Magnetic resonance imaging. If CT cannot definitively demonstrate the benign nature of an adrenal mass, further assessment is provided by 'chemical shift' sequences of MRI: a loss of signal on the out-of-phase images as compared with in-phase images is indicative of an adrenal adenoma.[7,18]

Nuclear medicine. Although not first-line investigations, nuclear medicine modalities may add information about the functional as well as the anatomical characterisation of the masses, providing additional information on coexistent tumours elsewhere.[7,18]

Fine-needle aspiration

At present, some 30% of adenomas may be indistinguishable from non-adenomas on both unenhanced CT and chemical shift MRI.[7,18] Masses characterised as non-adenomas on imaging, and thus of uncertain pathology, may require biopsy or surgical resection.[4] Fine-needle aspiration biopsy is a relatively safe procedure, but is contraindicated if there is a suspicion of primary adrenocortical carcinoma or phaeochromocytoma (unless pharmacologically blocked with adrenoceptor blockade).[23]

Surgical treatment or long-term follow-up

When the morphological features or hormonal profile suggest surgical removal of an adrenal incidentaloma, the laparoscopic approach is now used in most cases unless an adrenocortical carcinoma is strongly suspected. When the data from the biochemical tests and the imaging have been inconclusive, a 'wait-and-see' policy with interval imaging and biochemical retesting has been proposed.[22] Patients with tumours remaining stable on two imaging studies at least six months apart, and not exhibiting hormonal hypersecretion over four years, may not need further follow-up.[4,5,13,22]

Conclusions

Incidentally-discovered adrenal masses are seen increasingly frequently, and all clinicians need to be aware of their implications and management. Each case needs to be treated individually, taken in the context of the patient's age and general condition. In general, some 4% of CT scans reveal an adrenal incidentaloma (accepting this as a mean across all ages), some 4% of these are either phaeochromocytomas or adrenocortical cancers, a diameter of 4 cm is used to initiate mandatory removal and, finally, the current recommendation of follow-up is four years. We therefore suggest that 'a rule of four' for these tumours is a useful mnemonic for this common problem (with apologies to Sir Arthur Conan Doyle).

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Cushing's syndrome

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This article discusses endogenous Cushing's syndrome which is due to prolonged, inappropriate and excessive circulating free cortisol.[1] Exogenous glucocorticoids are a frequent cause so an adequate medication history is essential.

Epidemiology, prognosis and causes

Patients with severe Cushing's syndrome have a fivefold excess mortality. Reported prevalence is low (0.7–2.4/million population) with a mean of onset of 36 years. However, recent data show that 2–5% of obese patients with poorly controlled type 2 diabetes and hypertension have biochemical Cushing's and benefit from treatment for their cortisol excess.[2] This suggests that widespread screening for Cushing's syndrome in such populations may be warranted but it is not yet established. Causes of Cushing's syndrome are listed in Table 1.

Clinical features (Table 2)

Clinical features vary among patients and may fluctuate in a 'cyclical fashion' causing diagnostic difficulty. The signs most reliably distinguishing Cushing's from simple obesity are thin skin, easy bruising, proximal myopathy and, in children, decreased linear growth.[3]

Biochemical evaluation

Biochemical evaluation involves two steps:

- establishing a diagnosis of hypercortisolaemia
- defining the cause.

Biochemical diagnosis of hypercortisolaemia (Fig 1)

Clinical suspicion usually prompts evaluation, but certain patient groups may warrant screening,[1] for example:

- poorly-controlled, hypertensive patients with diabetes
- unexplained osteoporosis.

Hypercortisolaemia is also found in some patients with depression, alcohol dependence, anorexia nervosa and late pregnancy. In contrast to true endogenous Cushing's syndrome, in these situations the biochemistry improves when the underlying condition has resolved.

Table 1. Aetiology of Cushing's syndrome.

Cause	%	Female: Male	Female (%)	Male (%)
ACTH-dependent:				
Cushing's disease (pituitary)	70	3.5:1	90	60–70
Ectopic ACTH syndrome[a]	10	1:1	10	30
Unknown source of ACTH[b]	5	5:1		
ACTH-independent:				
Adrenal adenoma	10	4:1		
Adrenal carcinoma	5	1:1		
Macronodular hyperplasia	<2			
Primary pigmented nodular adrenal disease[c]	<2			
McCune Albright syndrome	<2			

[a]Most common causes: small-cell lung cancer, bronchial carcinoid tumours.
[b]Patients may ultimately prove to have Cushing's disease.
[c]Sporadic or as part of Carney complex (atrial myxoma, cutaneous lentigines, pituitary tumours – germline mutations of the regulatory subunit R1A of PKA *(PRKAR1A)* are present in approximately 45% of patients with Carney complex).