Subclinical endocrinological disease

Series editor: Dr JWF Elte, Department of Internal Medicine, Sint Franciscus Gasthuis, Rotterdam, The Netherlands

Adrenal incidentaloma: subclinical Cushing's syndrome

John Newell-Price, Ashley Grossman

Summary

Adrenal incidentalomas present a significant differential diagnostic challenge. All patients with an incidentally discovered adrenal lesion should be carefully considered and re-evaluated to exclude extra-adrenal malignancy. Tumours with hypersecretory syndromes require excision, whilst those tumours more than 6 cm in size, particularly if they exhibit other features of malignancy on computed tomography (CT), magnetic resonance imaging (MRI) or scintigraphy, should also be excised. In all cases screening for pheochromocytomas should be performed, and in the context of hypertension and spontaneous hypokalaemia, a primary aldosterone-secreting tumour requires exclusion. However, the natural history and treatment regimens for those individuals demonstrating 'subclinical Cushing's syndrome' is far from clear. Size, as determined by CT or MR scanning, does not in itself reliably distinguish benign from malignant disease. Scintigraphy may be a useful adjunct, with discordant patterns suggesting malignant disease. Fine needle aspiration should not routinely be used but may be useful in cases of doubt about other extra adrenal malignancy.

Keywords: adrenal incidentaloma, Cushing's syndrome, malignancy

Department of Endocrinology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK
J Newell-Price
AB Grossman

Correspondence to Professor AB Grossman

Accepted 16 October 1995

The extensive use of sophisticated diagnostic tools is generating an ever-increasing list of hitherto undisclosed clinical or subclinical disorders. The relevance of such conditions to clinical practice needs careful evaluation. This is never more apparent than in the case of the adrenal 'incidentaloma', a serendipitously discovered mass on an abdominal computer tomography (CT) scan performed for reasons other than investigating adrenal pathology, or for the staging of malignancy (box 1).

The vast majority of incidentalomas are non-secretory, benign lesions.¹ However, once discovered, two main questions arise: firstly, is the incidentaloma associated with a hypersecretory syndrome and, second, is the lesion benign or malignant (box 2)? Following the appropriate investigations surgical excision is required for those associated with a hypersecretory state, whilst controversy exists as to the optimum management of either non-secretory lesions, or lesions associated with sub-clinical hormone secretion.

Prevalence

Reported prevalences of adrenal incidentalomas on CT scanning performed for reasons other than the investigation of adrenal pathology vary from 0.6 to 1.9%.² This is lower than the 8.7% prevalence reported in *post-mortem* studies, in which there has been no documented evidence of adrenal dysfunction *ante mortem*.³ The reasons for this discrepancy are unclear, but it may well be that as scanning techniques improve the 'in life' prevalence is liable to rise.

Hypersecretion?

By definition, patients with an incidentaloma should not have clinical features of hormonal excess, although this needs to be carefully re-considered in the light of the imaging investigation. The relative chances of a specific pathological diagnosis, and the risk to the patient in terms of morbidity and mortality, affect biochemical and hormonal screening choices. It has been estimated that pheochromocytomas, primary aldosterone-secreting adenomas, adrenocortical adenomas and adrenocortical carcinomas will occur in 6500, 7000, 35 and 58, respectively, per 100 000 abdominal scans.² On this basis every patient with an incidentaloma, regardless of clinical criteria, should be screened for a pheochromocytoma and aldosterone-secreting adenoma, whilst the extensive investigation of subtle glucocorticoid excess remains controversial.

PHAECHROMOCYTOMA

In the context of an adrenal adenoma disclosed on imaging, the absence of episodes of hypertension has a negative predictive value of 96.5%, which may be elevated to 99.6% in the complete absence of any symptoms of catecholamine excess such as palpitations, abdominal pain, nausea and vomiting, nervousness or chest pain²; thus, if hypertension or symptoms are absent then the presence of a pheochromocytoma is highly unlikely. Pheochromocytoma is, however, a potentially lethal condition, and biochemical evaluation is required in all patients with an incidentaloma; normal 24-hour urinary vanillyl mandelic acid excretion, regardless of clinical details, has a negative predictive value of 98.2%,² although 24-hour urinary catecholamine excretion is superior to this as a screening test.⁴ Such biochemical evaluations should precede invasive procedures such as fine needle aspiration, biopsy or surgery, since hypertensive crises and death may be inadvertently precipitated in undiagnosed pheochromocytomas.^{5,6}

Adrenal incidentaloma

An adrenal mass disclosed by chance on abdominal CT or MRI scanning, being performed for reasons other than investigating adrenal pathology

Box 1

Box 2

Clinical features of Cushing's syndrome

Commonly quoted features:

obesity

hirsutism

hypertension

'buffalo hump'

moon facies

striae

diabetes mellitus

depression and psychosis

Most discriminating features:

proximal myopathy

thin skin

easy bruising

Box 3

1 mg overnight dexamethasone test

dexamethasone 1 mg po at 24.00 h

sample for plasma cortisol 08.00 h next day

48 h, 2 mg/day low-dose dexamethasone test

09.00 h sample for plasma cortisol

dexamethasone 0.5 mg po at 09.00 h and then 6 hourly for 48 h

then sample for plasma cortisol at 09.00 h

Box 4

PRIMARY ALDOSTERONE-SECRETING ADENOMAS
Nearly all patients with a primary aldosterone-secreting adenomas are hypertensive at the point of diagnosis.⁷ Thus, the serum potassium should be estimated in all patients with incidentalomas who are hypertensive, and if the serum potassium is greater than 3.5 mmol/l no further investigation is routinely required. If, however, there is spontaneous hypokalaemia, or extreme diuretic-induced hypokalaemia (less than 3.0 mmol/l), further evaluation following salt loading should be performed with paired 08.30 h recumbent and 4-hour ambulatory plasma renin and aldosterone estimation.⁸ A suppressed plasma renin activity and a high plasma aldosterone when recumbent that falls following ambulation is supportive evidence of an adenoma.

GLUCOCORTICOID EXCESS AND 'SUBCLINICAL CUSHING'S SYNDROME'
It is now well documented that many incidentalomas, previously considered to be non-functional, display subtle derangements of the hypothalamo-pituitary-adrenal axis, dubbed 'pre-Cushing's syndrome' or 'subclinical Cushing's syndrome'.⁹⁻¹⁵ Although the prevailing plasma cortisol in these individuals is insufficient to cause the protean clinical manifestation associated with the hypercortisolaemia of Cushing's syndrome (box 3), or fully suppress circulating plasma adrenocorticotropin, adrenal insufficiency has been described following excision of these tumours.¹¹ Such hypothalamo-pituitary-adrenal axis abnormalities are more common in those individuals with hypertension, obesity and diabetes.^{2,13}

The recommendations for the investigation and treatment of clinically florid Cushing's syndrome are varied and often contradictory.^{16,17} It is thus not surprising that debate exists over the optimum investigation of subclinical Cushing's syndrome. It does, however, appear that the use of 24-hour urinary free cortisol excretion is not a sensitive indicator of this low grade hypercortisolaemia,¹³ whilst non-suppression on dexamethasone testing has been reported in many studies.^{9-11,13} Most reports utilise the 1 mg overnight dexamethasone suppression test (box 4), in which failure of suppression of the plasma cortisol following the administration of dexamethasone is consistent with the diagnosis of Cushing's syndrome. Interestingly, there appears to be no correlation between the response to dexamethasone and the size of tumour on scanning.¹⁸ However, in the evaluation of Cushing's syndrome this test is inferior (with more false negatives) to the standard 48-hour 2 mg/day low-dose dexamethasone suppression test (box 4).¹⁶ It is highly likely, therefore, that the 2 mg/day test would be more reliable in the context of subclinical Cushing's syndrome, allowing disclosure of more subtle derangements of the hypothalamus-pituitary-adrenal axis, although this is yet to be fully determined. Loss of circadian rhythm of cortisol has been reported, although its widespread use has not been advocated.¹³ A detectable sleeping midnight plasma cortisol has a higher sensitivity than the low-dose dexamethasone suppression test in the investigation of clinically overt Cushing's syndrome, especially in cases of lower mean plasma cortisol levels.¹⁹ It is thus likely that this test may disclose even more subtle derangements of the hypothalamo-pituitary-adrenal axis, but requires in-patient evaluation that may not be justified in the context of an incidentaloma.

Recently, a low plasma dihydroepiandrosterone sulphate has been shown to be associated with plasma cortisol non-suppressibility on dexamethasone testing in a series of incidentally discovered benign adrenal adenomas, whilst it was elevated in two cases of adrenal cortical carcinomas.¹⁵ The secretion of dihydroepiandrosterone sulphate is stimulated by adrenocorticotropin. It has thus been proposed that the autonomous secretion of cortisol by these adenomas is sufficient to suppress plasma adrenocorticotropin, and hence lower the values of dihydroepiandrosterone sulphate, whilst carcinomas can have alterations of their steroid synthetic pathways and hence preferentially secrete dihydroepiandrosterone sulphate and other steroids. Overall, the combination of an overnight 1 mg low-dose dexamethasone suppression test and plasma dihydroepiandrosterone sulphate estimation has been advocated as a screening test for subclinical Cushing's syndrome, and to suggest benign disease. Whilst this seems a reasonable policy, we would recommend the utilisation of the standard 2 mg/day low-dose dexamethasone suppression test rather than the overnight 1 mg dexamethasone suppression test. Nevertheless, it remains unknown as to how many of these lesions will progress to clinically significant Cushing's syndrome, and it is unclear at what stage adrenalectomy should be considered for these adenomas. If evidence of autonomous cortisol secretion is disclosed on testing such operations should be performed with glucocorticoid cover. Certainly, careful clinical, biochemical, and imaging follow-up is required.

Benign or malignant?

The adrenal glands are highly vascular organs, and therefore are common sites of metastases from extra-adrenal malignancy. Thus, in all cases of non-secretory adrenal incidentalomas the possibility of an extra-adrenal primary neoplasm should be considered. Various criteria have been studied in an effort to distinguish benign from malignant primary adrenal disease.

SIZE

Some benign adrenal masses, such as myolipomas, simple cysts and haemorrhage, are identifiable on CT and require no further evaluation,^{1,2,20} although partially cystic lesions merit evaluation as malignancy is more likely and haemorrhage into a carcinoma may also occur.²¹ If no obvious characteristics are present, the size of the lesions *per se* has been quoted as indicative of malignancy. The size recommendation 'cut-offs' for benign disease, however, varies from 3–6 cm,^{2,22,23} with the recommendation for excision of lesions greater than these diameters, regardless of CT or needle aspiration characteristics. Although the chances of malignancy increase with size, this is in itself a poor discriminator since in masses of greater than 4 cm there is still a benign to malignant ratio of 8:1,²⁴ whilst malignant lesions less than 2.5 cm have been described.²⁵ The most widely accepted diameter differentiating predominantly benign from malignant lesions is 6 cm.²²

IMAGING CHARACTERISTICS

Much effort has gone into attempts to differentiate between benign and malignant disease on radiographic appearances. A benign adenoma is best characterised on CT scanning by a small, well-circumscribed lesion, with a low, homogeneous attenuation signal; in contrast, malignancy is suggested by larger non-homogeneous lesions, with poorly defined margins, particularly if there is evidence of vascular invasion.^{1,20}

These appearances are, however, by no means invariable. Magnetic resonance imaging (MRI) has been used in an effort to characterise adrenal masses, but there is an approximately 30% overlap between malignant and benign disease on both T1 and T2-weighted spin echo images.²⁶ It was hoped that chemical-shift MRI would discriminate between the high lipid content of benign lesions, such as adenomas or myelolipomas, from those with low lipid contents such as metastases, haemorrhages, pheochromocytomas and cysts; however, this has not been reproduced in later studies.²⁷

Thus neither CT nor MRI characteristics, in themselves, will reliably differentiate between benign and malignant disease.

SCINTIGRAPHY

Over the past decade the use of ¹³¹I-6-β-iodomethylnorcholesterol (NP-59) adrenal scintigraphy has been advocated to distinguish benign from malignant new adrenal masses. Lipid-rich, functional adrenal tissue, such as a benign adrenal adenoma, demonstrates preferentially increased uptake that is concordant with (ie, on the same side as) the anatomical lesion displayed on CT or MR scanning. In contrast, discordant scintigraphy, with uptake on the contralateral side to the anatomical lesion illustrated on CT or MR scanning, has been shown to predict metastatic disease, primary adrenal malignancy, or cystic disease.²⁸ However, lesions of less than 2 cm in diameter are not reliably discriminated by this technique.²⁵ In most institutions this scintigraphic technique has not gained widespread popularity, mainly because of high costs and insufficient experience: it remains a potentially useful diagnostic adjunct.

FINE NEEDLE ASPIRATION

Fine needle aspiration under CT guidance may provide a definitive histological diagnosis, but is most effective at distinguishing between adrenal and non-adrenal tissue, and thus in distinguishing primary adrenal malignancy from metastases.⁶ Analogous to a follicular adenoma of the thyroid, it is not possible, on this test alone, to differentiate between a primary adrenal adenoma and carcinoma, as the latter requires evidence of capsular or vascular invasion. There is a significant morbidity associated with this procedure (for example, haemorrhage, pneumothorax, pancreatitis) and it should thus be reserved for cases of doubt, and is not indicated where a hormonally active tumour has been identified, particularly if this is suspected to be a pheochromocytoma.²⁸

Conclusions

Adrenal incidentalomas present a significant diagnostic challenge, and it seems likely that their prevalence will increase. The natural history of the vast majority

of these lesions is unknown and thus guidelines for management will continue to evolve for some time to come. At present certain recommendations may be made.

All patients with an incidentally discovered adrenal lesion should be carefully considered and re-evaluated to exclude extra-adrenal malignancy. In all cases, screening for phaeochromocytomas should be performed utilising 24-hour urinary catecholamine estimation. In the context of hypertension and spontaneous hypokalaemia, paired recumbent and 4-hour ambulatory plasma renin activity and aldosterone measurements should be performed for the exclusion of a primary aldosterone-secreting tumour. A low-dose dexamethasone suppression test and plasma dihydroepiandrosterone sulphate level should be performed, although the natural history and treatment regimens for those individuals demonstrating 'subclinical Cushing's syndrome' is far from clear. A pragmatic plan would be for interval clinical and biochemical follow-up, together with further scanning if these parameters change.

Size, as determined by CT or MR scanning, does not in itself reliably distinguish benign from malignant disease. Other criteria such as an anatomical shape and tissue density, or signal intensity, may help. Low CT attenuation is suggestive of a benign lesion, and appears to be as good as any MR signal sequences. Scintigraphy may be a useful adjunct, with discordant patterns suggesting malignant disease, but cost and inexperience of the technique may limit its widespread application.

Tumours with hypersecretory syndromes require excision, whilst tumours more than 6 cm in size, particularly if they exhibit other features of malignancy on CT, MR or scintigraphy, should also be excised. Smaller tumours with questionable features of malignancy and equivocal scintigraphy features (if performed) are probably best followed by interval scanning at a period of some 3–6 months. Fine needle aspiration should not routinely be used but may be useful in cases of doubt about other extra-adrenal malignancy.

We thank Ella Marcar for her secretarial assistance in the preparation of this manuscript.

- Dunnick NR. Adrenal imaging: current status. *AJR* 1990; 154: 927–36.
- Ross NS, Arron DS. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. *N Engl J Med* 1990; 323: 1401–5.
- Hedeland H, Ostberg G, Hokfelt B. On the prevalence of adrenocortical adenomas in an autopsy material in relation to hypertension and diabetes. *Acta Med Scand* 1968; 184: 211–4.
- Ross GA, Newbold EC, Thomas J, et al. Plasma and 24 h-urinary catecholamine concentrations in normal and patient populations. *Ann Clin Biochem* 1993; 30: 38–44.
- Shapiro B, Fig LM. Management of phaeochromocytomas. *Endocrinol Metab Clin N Am* 1989; 18: 443–81.
- Candel AG, Gattuso P, Rayes CV, Prinz RA, Castelli MJ. Fine-needle aspiration biopsy of adrenal masses in patients with extra adrenal malignancy. *Surgery* 1993; 114: 113–27.
- Melvi JC. Diagnosis and treatment of primary aldosteronism and isolated hypo-aldosteronism. *J Clin Endocrinol Metab* 1985; 14: 977–95.
- Wineburger NH, Fineberg NS. The diagnosis of primary aldosteronism and separation of two major sub-types. *Arch Intern Med* 1993; 153: 2125–9.
- Bogner U, Eggens U, Henson J, Oelkers W. Incidentally discovered ACTH-dependent adrenal adenoma presenting as 'pre-Cushing's Syndrome'. *Acta Endocrinol* 1986; 111: 89–92.
- Beyer HS, Doe RP. Cortisol secretion by an incidentally discovered non-functional adrenal adenoma. *J Clin Endocrinol Metab* 1986; 62: 1317–21.
- Huiras CM, Pehling GB, Caplan RH. Adrenal insufficiency after operative removal of apparently non-functioning adrenal adenomas. *JAMA* 1989; 261: 894–8.
- Rosen HN, Swartz SL. Subtle glucocorticoid excess in patients with an adrenal incidentaloma. *Am J Med* 1992; 92: 213–6.
- Rinke M, Niekke J, Krestin GB, Saeger W, Allolio B, Winkelmann W. Pre-clinical Cushing's syndrome in adrenal 'incidentalomas': comparison with adrenal Cushing's syndrome. *J Clin Endocrinol Metab* 1992; 75: 829–32.
- Caplan RH, Strutt PJ, Wickus GG. Sub-clinical hormone secretion by incidentally discovered adrenal masses. *Arch Surg* 1994; 129: 291–6.
- Osella G, Terzolo M, Borretta G, et al. Endocrine evaluation of incidentally discovered adrenal masses (incidentalomas). *J Clin Endocrinol Metab* 1994; 79: 1532–9.
- Trainer PJ, Grossman AB. Investigation of Cushing's syndrome. *Clin Endocrinol* 1991; 34: 317–30.
- Orth DN. Cushing's syndrome. *N Engl J Med* 1995; 332: 791–803.
- Charbonnel B, Shatal JF, Ozanne P. Does the cortical adrenal adenoma with 'pre-Cushing's' syndrome exist? *J Nucl Med* 1981; 22: 1059–61.
- Newell-Price JDC, Trainer PJ, Perry LA, Wass JAH, Grossman AB, Besser GM. A single sleeping midnight cortisol has 100% sensitivity for the diagnosis of Cushing's syndrome. *Clin Endocrinol* 1995; 43: 545–50.
- Frances IR, Gross MD, Shapiro B, Korobkin M, Quint LE. Integrated imaging of adrenal disease. *Radiology* 1992; 184: 1–13.
- Sakamoto I, Nakahara N, Fukuda T, Magayoshi K, Matsunaga N, Hayashi T. A typical appearance of adrenal pseudo-cysts. *J Urol* 1994; 152: 150–2.
- Copeland PM. The adrenally discovered adrenal mass. *Ann Intern Med* 1983; 98: 940–5.
- Gross MD, Shapiro B, Bouffard JA, et al. Distinguishing benign from malignant euadrenal masses. *Ann Intern Med* 1988; 109: 613–8.
- Herrera MF, Grant CS, van Heeredn JA, Sheedy PF, Listrup DM. Incidentally discovered adrenal tumours: an institutional perspective. *Surgery* 1991; 110: 1014–21.
- Gross MD, Shapiro B, Francis IR, et al. Scintigraphic evaluation of clinically silent adrenal masses. *J Nucl Med* 1994; 35: 1145–52.
- Remer EM, Weinfield RM, Glazer GM. Hyperfunctioning and non-hyperfunctioning benign adrenal cortical lesions; characterisation and comparison with MR imaging. *Radiology* 1989; 171: 681–5.
- Kloos RT, Shapiro B, Gross MD. The adrenal incidentaloma. *Curr Opin Endocrinol Diabetes* 1995; 2: 222–30.