Adrenal incidentaloma

Prevalence
5% post-mortem series
4% CT series
6-20% CT series in patients with Hx extra-adrenal malignancy
Commoner with increasing age
Associated with adrenal hyperfunction in 15%
  - Phaeochromocytoma (1-11% of AI) – tachycardia, high BP, flushing
    may be present but not necessarily. etc
  - Conn’s syndrome – (1-3.3%) hypertension, hypokalaemia
  - Cushing’s syndrome – central obesity, striae, High BP/Glu, Low K+
  - Androgen secreting tumours – rare, hirsutism, virilisation etc.
Non-functioning tumours in 85%

What are the chances of it being cancer?

<1% chance of being a met with no prior history of primary cancer
<5% chance of being a primary adrenal cancer
? chance of being a met with a known primary

Investigation and management focused on determining likelihood of functioning tumour and malignancy

Investigation
History and clinical examination suggesting functioning tumour
Biochemical testing

24 hour urinary catecholamines/metanephrines [Alternatively plasma free metanephrines: higher sensitivity (99%) cf. urinary catecholamines (86%) and metanephrines (77%); but difficult to get Lerner 2002]

Aldosterone-renin ratio. Good test for Conn’s but aldosterone should be high normal or high (low renin with normal aldosterone gives elevated ARR in low-renin essential hypertension. Must stop beta-blockers (false-positives) and aldosterone antagonists (false negatives)
If ARR high, needs salt-loading test to confirm diagnosis because of significant daytime variation
Selective venous sampling recommended to localise tumour - 50% concordance with CT over ?unilateral or bilateral Nwariaku 2006
Alternatively radiolabelled cholesterol (131-I iodocholesterol ) scintigraphy, but poor uptake in small tumours

1mg dexamethasone overnight suppression test. 1mg DXM at 11pm, bloods at 8am. Using modern radioimmunoassay, most patients with normal adrenals do not produce cortisol. Therefore <138nmol/l = equivocal;
>138nmol/l = autonomous glucocorticoid hypersecretion. AGH is called Cushings if clinical features present or subclinical (SAGH) if no features
SAGH seen almost exclusively in patients with adrenal incidentalomas 12.5% risk of developing Cushings’ at 1 year.

Computed tomography
Risk of adrenal cancer related to size: 2% <2cm; 6% 4-6cm; 25% 6cm+
Calcification, necrosis and haemorrhage rarely seen in benign tumours
Attenuation value <10HU 98% specific for benign adenomata (Singh 2008)
Adrenal incidentaloma

>50% washout of contrast medium after 10 mins has sn/sp of 95-98% for benign adenomata (Caoili 2002)
Controversial results suggesting MRI any better or worse than properly performed CT with 10 min washout
MRI does not rely on gadolinium washout, rather loss of signal after RF pulse. Fat loses signal rapidly.
PET scanning – may be useful in patients with known primary cancer.

Fine-needle aspiration cytology
Most commonly used in patients with AI and a history of extra-adrenal carcinoma. Typically in situations where PET unavailable. Largest series of 277 patients; sensitivity 81% (false negative 19%), specificity 99%. Complication rate 2.8% (Welch 1994). NB. Phaeo must be excluded prior to FNAC to avoid hypertensive crisis.

Management strategies
Adrenalectomy for:
Functioning tumour
Non-functioning tumour > 6cm
Non-functioning tumour < 6 cm with calcification, haemorrhage or necrosis
Non-functioning tumour with positive PET or FNAC if solitary and appropriate in context of primary tumour

Follow-up for all others
Follow-up considerations
Non-functional to functional – 2-8% within 2 years (usually AI > 3cm)
Growth rate >1cm in 5-25% of incidentalomas. Of these 5% malignant when excised for increased growth alone.
No formal follow-up schedule validated.
Re-imaging at 6 months, 12 months and 24 months with repeat biochemical testing yearly

Suggested algorithm
Appendix

Anatomy
Adrenal 5 x 3 x 1cm in length
Weight 5 g
Cortex from mesoderm; medulla from neurectoderm
Cortex ~90% tissue; from out to in;
- Zona glomerulosa mineralocorticoids (aldosterone)
- Zona fasciculata glucocorticoids
- Zona reticularis androgens and oestrogens
Cortex enlarged in fetus? why
Medulla 10% tissue noradrenaline and adrenaline
Blood supply
- Arterial Main supply inferior phrenic
  Additional branches from renal artery & aorta
- Venous Right = common apical vein drains into IVC. Occasionally receives an aberrant unnamed hepatic branch vein
  Left = common vein drains into renal vein opposite gonadal. Usually receives drainage from inferior phrenic coursing medially

Physiology

Major androgens DHEA, DHA sulphate and androstenedione
Cortisol release regulated by hypothalamus-pituitary-adrenal axis via corticotrophin releasing hormone, producing ACTH from anterior pituitary
Cortisol release diurnal - peak at ~ 0600, trough at ~ midnight
Aldosterone release stimulated by angiotensin II (less important secondary response to low potassium – inhibits release)
Adrenal medulla hormones synthesised from phenylalanine in following order:
  phenylalanine – tyrosine – L-Dopa – dopamine – noradrenaline – adrenaline
  Dopamine, NA and Adr considered catecholamines, others precursors. NA comprises ~70% total stored catecholamines (15% each for others)
Half-life catecholamines ~20s; broken down by MAO and catechol methyltransferase; largest metabolite urinary VMA
Selected adrenal disorders

(i) Cushing’s syndrome

Central obesity, moon face, thin skin, bruising, striae, hirsutism, hypertension, diabetes etc.

Causes

Endogeneous (steroid administration commonest cause)

Endogenous

Pituitary tumours (Cushing’s syndrome)* 68%

Ectopic ACTH production* 12%

Adrenal adenoma 10%

Adrenal carcinoma 8%

* ACTH dependent. Lung cancer accounts for > 50% ectopic ACTH production (invariably due to tumour)

Diagnosis

Blood sampling

1. 24 hour cortisol secretion on 3 occasions most reliable estimate of cortisol secretion

2. Midnight ACTH-cortisol measurement on 2 occasions – determines whether ACTH dependent (pituitary/ectopic) or ACTH independent (adrenal)

3. High dose DXM suppression test (2mg qds 2 days – measure plasma cortisol) – distinguishes pituitary from ectopic ACTH.

Radiographic imaging (adrenal/pituitary)

Adrenal tumours >5cm, calcification, necrosis haemorrhage suggestive of carcinoma vs adenoma

High signal intensity on T2 weighted images also highly suggestive of malignancy

Management

Pituitary disease

Transphenoidal hypophysectomy

Radiation for surgery failures

Ectopic production

Treat primary tumour

(ii) Adrenocortical carcinoma

Even after surgical removal differentiating benign from malignant adrenal lesions may be difficult – Weiss criteria designed to assist pathologists

High mitotic rate (>5 per 50 high-power field)

Atypical mitoses

Venous invasion

High nuclear grade (Fuhrman 3-4)

Absence of cells with clear cytoplasm (<25% of cells)

A diffuse growth pattern (more than one third of tumor)

Necrosis

Sinusoidal invasion

Capsular invasion

Three or more are needed for diagnosis of carcinoma.
Carcinoma
Non-functional in 40%; functional in 60% (of these 60% Cushing’s syndrome)
With exception of rare testosterone-secreting tumours, highly malignant with 5YS ~35%. Early metastasis to lungs, liver, lymph nodes common; local invasion typical
Rx = **surgical extirpation** – improved survival with complete excision
Radiotherapy only for palliation; chemoresistant (p-glycoprotein)

(iii) **Conn’s syndrome** (primary hyperaldosteronism)
1-2% of hypertensive patients
Adenoma >> carcinoma
Hypertension, hypernatraemia, hypokalaemia and alkalosis
Oedema not a feature due to ‘mineralocorticoid escape’
**Hypertension, low plasma renin activity (PRA) and high aldosterone hallmarks of diagnosis** (differentiates secondary from primary aldosteronism)
Diagnosis with ARR (see above) – confirm with salt loading test and postural stimulation test. Lateralisation using CT +/- adrenal vein sampling
Management
  - Idiopathic hyperaldosteronism medical with spironolactone or amiloride
  - Autonomous focus adrenalectomy

(iv) **Multiple endocrine neoplasia**
MEN 1 Autosomal dominant defect MEN 1 gene chromosome 11
Pituitary, parathyroid hyperplasia and pancreatic tumours
MEN 2a Parathyroid hyperplasia, medullary C-cell thyroid carcinoma, phaeochromocytoma
  2b Medullary C-cell thyroid carcinoma, phaeochromocytoma, marfanoid, neurofibromas