HYPOADRENALISM

Inadequate cortisol and/or aldosterone secretion (1^0 = adrenal disease (ACTH rises); 2^0= ACTH deficiency)

AETIOLOGY: 1^0 HYPOADRENALISM (ADDISON'S DISEASE)

1. AUTOIMMUNE ADRENALITIS (80%)

Adrenal cortex atrophy w/ intact medulla||Autoabs vs: 21-OHase, ACTH receptor, Ags on other steroidogenic cells

2. TB: gland enlarges with caseating granulomata → fibrosis and calcification

3. HIV/AIDS

Less common:

1. METASTASES
2. ADRENAL VEIN THROMBOSIS
3. INTRA-ADRENAL HAEMORRHAGE: Waterhouse-Friedrichson syndrome in meningococcal septicaemia
4. LYMPHOMA
5. AMYLOIDOSIS
6. HEREDITARY ADRENOCORTICAL NON-RESPONSIVENESS TO ACTH
7. HAEMOCHROMATOSIS
8. BILATERAL ADRENALECTOMY
9. CONGENTIAL ADRENAL HYPERPLASIA
10. DRUGS (metyrapone, ketoconazole, etomidate, aminoglutethimide, rifampicin, phenytoin, opiates)

AETIOLOGY: 2^0 HYPOADRENALISM

1. SUDDEN WITHDRAWAL OF GLUCOCORTICOID TREATMENT WITH FAILURE TO REPLACE

Suppressed HPAc axis → ACTH suppressed →adrenal atrophy → cortisol suppressed

2. SECONDARY TO **HYPOTHALAMIC/PITUITARY DISEASE** WITH LOW CRH/ACTH

CLINICAL FEATURES

1. SKIN PIGMENTATION

Due to elevated ACTH (only if progressive adrenal destruction, not if rapid) (always in 1^0, never in 2^0 disease)

3 hormones derived from POMC (pro-opiomelanocortin) contain MSH sequences

Sun-exposed areas, recent scars, nipples, axillae, palmar creases, pressure points, mucous membranes

2. VITILIGO

3. WEIGHT LOSS/WASTING

4. GI UPSET (ABDO PAIN/N&V/DIARRHOEA)

5. HYPOTENSION (loss of mineralocorticoids +loss of glucocorticoid-mediated vasoconstriction)

6. GONADAL FAILURE (in hypothalamic/pituitary disease)

(a)Intact mineralocorticoid production/secretion (b)Isolated ACTH deficiency → low cortisol without pigmentation

7. ACUTE ADRENAL CRISIS: Shock, cramps, N&V, diarrhoea, fever, convulsions; hyponatraemia/hyperkalaemia

ELECTROLYTE DISTURBANCES: Hyponatraemia/Hyperkalaemia/Hypercalcaemia/Hyperuraemia/Hypoglycaemia

HAEMATOLOGICAL FEATURES: Eosinophilia/Neutropaenia/Lymphocytosis

BASIC INVESTIGATIONS **(diagnosis, cause and effect!)**

Bloods (FBC, U&E, Ca2+, AutoAb screen/HIV test)

(serum cortisol) (serum ACTH) (lying/standing serum aldosterone and renin)

Urinary free cortisol

CBG

Blood pressure

0900 plasma ACTH elevated with low/normal cortisol implies 1^0 hypoadrenalism

SPECIAL TESTS

1. SHORT SYNACTHEN/ACTH STIMULATION TEST

Exogenous ACTH administered and measure serum cortisol; both primary and secondary disease will fail to respond
Measure ACTH to differentiate between 1^0 and 2^0

2. LONG SYNACTHEN TEST

1mg tetracosactide 24hr; 2^0 = progressive cortisol increase w/ repeated ACTH administration; 1^0 fails to respond

3. CRH STIMULATION: Give CRH and assess for ACTH response (pit disease= no ACTH response)

4. STRESS TEST: Give insulin to see if ACTH and cortisol rise in response (tests whole HPA axis)

5. MINERALCORTICOID AXIS

(a)Lying: PRA and PAC (b)Standing: in mineralocorticoid deficiency, PRA rise with failure of PAC response

MANAGEMENT

1^0 need GC and MC replacement

2^0 need GC alone

30mg hydrocortisone daily (20mg AM, 10mg PM) at both 6 o'clocks
Double dose when ill, stressed, on enzyme-inducing drugs, pregnant
In Addison's, fludrocortisone 0.3mg/day and monitor BP/electrolytes/renin

Acute adrenal insufficiency:

Normal saline 1L over 60 mins
100mg iv hydrocortisone ASAP and 6 hourly until stable then 50mg 6 hourly over 24 hours
Glucose
Oral replacement in TDS dosing then divided doses over few days
Introduce fludrocortisone later (when hydrocortisone being reduced)

Perioperative cover

Minor:
Major: hydrocortisone 100mg iv QDS then 50mg then stop

HYPERADRENALISM

Cushing's syndrome: *signs and symptoms of (a) prolonged exposure to inappropriately raised free plasma cortisol or (b) excessive glucocorticoid receptor activation*

Cushing's disease: *pituitary dependent bilateral adrenal hyperplasia → cortisol excess*

Rare (incidence 1/1,000,000/yr in the West)

Classification:

ACTH DEPENDENT

1. CRF: (i) hypothalamic adenoma (ii) ectopic CRF
2. ACTH (i) Cushing's disease (80%) (ii) ectopic ACTH (eg small cell bronchial ca) (iii) exogenous ACTH (synacthen)

ACTH INDEPENDENT

1. Exogenous glucocorticoids; **overall commonest cause of hypercortisolism**)
2. Adrenocortical adenoma/carcinoma
3. Carney's syndrome (ACTH receptor autoabs → primary pigmented nodular adrenocortical dysplasia, PPNAD)
4. ACTH-independent macronodular adrenal hyperplasia (AIMAH)
5. McCune-Albright (constitutively active ACTH receptor)

OTHER

GIP hypersensitivity (enhanced adrenal responsiveness to GIP)

Alcohol-associated pseudo-Cushing's syndrome (inhibition of 11B-HSD)

Clinical features:

Metabolic: diabetes/centripetal obesity with moon face and buffalo hump

Skin: thinning with bruising, striae/ACTH → pigmentation

Muscle: wasting and weakness (proximal myopathy)

Bone: Osteoporosis (involution of bone with deranged calcium absorption/excretion)

Immunosuppression (hides sepsis, latent infections re-activate, previous diseases worsen)

Hypertension (vasoconstriction, overcomes 11B-HSD → fluid retention and loss of K+ with alkalosis)

Mood changes (mania, depression, lethargy, loss of libido)

Androgen excess (hirsutism, virilism, acne, menstrual disturbances)

*pigmentation is common with ectopic ACTH but rare in Cushing's disease

*ectopic ACTH tumours: no residual negative feedback sensitivity to cortisol/stim with dex-suppression (unlike pituitary tumours); hypokalaemic alkalosis due to overcoming 11B-HSD barrier; if malignant, occurs too rapidly for clinical features; if benign tumour, slow-growing so clinical features develop

INVESTIGATIONS FOR CUSHING'S SYNDROME

(A)Exclude exogenous steroids as a cause first then one of three tests:

1.24 hr urinary free cortisol: reflects avg. plasma cortisol; 4x normal=CSyn; 3 samples (GC secretion intermittent)

2. Late-night salivary/plasma cortisol: lose cortisol secretion circadian rhythm

Resting midnight plasma cortisol >50nmol/L 100% sensitive for CSyn; salivary cortisol 92% sensitive

3. Low-dose overnight dexamethasone suppression test: loss of negative feedback loop in Cushing's syndrome

-dex binds cortisol receptors in pituitary, inhibits ACTH secretion; give at midnight to suppress plasma cortisol at 9am

-at 50nmol/L cut-off, 95% sensitive and 80% specific for Cushing's syndrome; 48hr test has greater specificity

False positives/negatives: critical illness, alcoholism, depression, drugs, renal failure, pregnancy, psychological stress

(B)NEXT: ACTH DEPENDENT OR INDEPENDENT?

Plasma ACTH measured on more than one occasion

-should be suppressed by negative feedback in ACTH independent Cushing's syndrome

-elevated in ACTH-dependent (higher in ectopic than pituitary disease; ?hypothalamic disease)

(C1)ACTH-DEPENDENT CUSHING'S DISEASE

1. CRH test: exaggerated increase in ACTH and cortisol in pituitary disease

-Adrenal tumours and ectopic ACTH will not respond (some ectopics do, reducing specificity)

**differentiates Cushing's disease from ectopic ACTH and adrenal tumours*

2. Inferior petrosal sinus sampling (IPSS)

-Both sinuses catheterised, CRH infused to avoid missing episodic ACTH secretion

-Basal IPSS:peripheral plasma ACTH >2 + CRH-stimulated IPSS:peripheral plasma ACTH >3 = Cushing's disease

**distinguish pituitary from ectopic ACTH (measure peripheral plasma ACTH simultaneously)*

3. High-dose dexamethasone suppression test

-Pituitary tumours retain some negative feedback absent in ectopic ACTH; won't exist in ACTH-independent disease

-Reduction of plasma cortisol <50% baseline (dexamethasone 8mg (or 2mg QDS for 48 hrs) = pituitary disease

**differentiate pituitary disease from ACTH-independent disease eg tumours, and ectopic ACTH*

(C2)ACTH-DEPENDENT CUSHING'S

Pituitary MRI: microadenoma not visible; non-func adenomas in 10% population (interpret with biochem tests)

CT NTAP: ectopic ACTH

Octreoscan: if primary not found on CT/MRI

(C3)ACTH-INDEPENDENT CUSHING'S

Adrenal disease: CT/MRI (malig risk: >4cm, high attenuation, heterogenous, irreg outline, delayed contrast washout)

MRI: gadolinium enhancement utilise higher water content of carcinoma

AIMAH: bilateral nodular adrenal hyperplasia seen on CT/MRI

PPNAD: may appear normal in Carney's syndrome

MANAGEMENT

ACTH-DEPENDENT CUSHING'S SYNDROME

SURGERY:

Trans-sphenoidal surgery (TSS) for pit adeno: less success for larger adenomas; repeat but risks panhypopituitarism

(a)alternative to re-operation: radiotherapy/stereotactic radiosurgery (gamma knife)/bilat adrenalectomy

**bilateral laparoscopic adrenalectomy has 95% remission rate with comparable QoL to TSS but loss of negative feedback → ACTH effects eg pigmentation and enlargement of ACTH tumour (Nelson's syndrome), reduced by neo-adjuvant radiotherapy

** radiotherapy has delayed effect on cortisol;risks panhypopituitarism

MEDICAL: for ectopic ACTH tumour: ketoconazole, metyrapone, aminogluthethimide, mitotane all inhibit cortisol production or secretion; metyrapone and mitotane favoured in small-cell lung cancer

ACTH-INDEPENDENT CUSHING'S

Unilateral adrenal lesion: **adrenalectomy**

Remaining gland suppressed so cover with glucocorticoids + synacthen test before withdrawal of glucocorticoids

HYPERALDOSTERONISM

Def: signs and symptoms of mineralocorticoid excess

Primary: adrenal disease → excessive production of aldosterone

Secondary: elevated renin drives aldosterone (renal hypoperfusion eg RAS; oestrogen eg during pregnancy; CCF; cirrhosis; accelerated hypertension) → treated with ACEis and spironolactone

Syndrome of apparent mineralocorticoid excess: primary hyperaldosteronism w/ low renin and aldosterone due to reduced 11BHSD levels (congenital), reducing cortisol → cortisone in kidney and thus normal cortisol levels can activate mineralocorticoid receptors, over the aldosterone in blood (acquired form due to liquorice/carbenoxolone inhibiting 11 BHSD)

PRIMARY HYPERALDOSTERONISM

1. Adrenal adenoma ie Conn's disease (80%, female)
2. Bilateral adrenal hyperplasia (30%, male)
3. Familial glucocorticoid-suppressible hyperaldosteronism

ACTH regulatory component of 11B-Hydroxylase fuses with aldosterone synthase gene

Aldosterone under ACTH control so responsive to steroid suppression

4. Adrenocortical carcinoma secreting aldosterone
5. 17aOHase def/11BOH def
6. Unilat adrenal hyperplasia

Clinical features

Hypertension (without oedema) usually only clinical sign

Hypokalaemia symptoms (alkalosis-->**paraesthesiae**+**tetany**; **polyuria**+**polydipsia** due to nephrogenic DI; palpitations)

Hypernatraemia symptoms (**muscle weakness**, **cramps**)

Investigations

(1) PRA (plasma renin activity) and **PAC** (plasma aldosterone concentration)

Stop beta-blockers and aldosterone-antagonists/correct hypokalaemia before testing

Lie down for 30 mins and measure PRA and PAC; Sit upright: Renin fails to respond

PAC:PRA of 20-30/suppressed PRA/elevated PAC → these 3 diagnostic of 1^{o} hyperaldosteronism

(2)Electrolytes:

Hypokalaemia

Hypernatraemia (may be low/normal in secondary aldosteronism as it may be part of the cause)

Metabolic alkalosis (loss of H+ in tubule/lack of K+ gradient across cells) so low bicarb due to shifts

(3)Urine: High aldosterone/high potassium/low sodium

Differential diagnosis

If suppressed renin and elevated aldosterone, Conn's must be differentiated from BAH by testing

Response of aldosterone to AT2: no increase in aldosterone in standing if Conn's and renin still low

Localisation

1.CT/MRI: good for tumours of 7mm+

2.Adrenal scintigraphy (OctreoScan?)

3.Bilateral adrenal vein catheterisation (via IVC): lateralisation: sensitivity 95% and specificity 100%

*recommended when considering surgery

Management

Surgery: for **unilateral** disease (Conn's/ACC/UAH)

Medical: spironolactone/ACEis in **bilateral** disease (GCSA/BAH/enzyme deficiencies) + steroids to suppress ACTH in GCSA

*medical therapy if (a)unfit for/declines surgery (rule out malignancy first) (b) all bilateral causes

ADRENOCORTICAL CARCINOMA

Incidence: 1-2,000,000/yr

(a)Most sporadic;

(b)Some associations with rare syndromes (MEN 1, Beckwith Wiedemann syndrome, Li-Fraumeni syndrome)

Clinical features

Most **hormonally functional** (1^0 Cushing's, 1^0 hyperaldosteronism, virilisation/feminisation)

Characteristically secrete **multiple hormones**

Biochemical diagnosis

Steroid secretory profile (especially multiple steroid hormones): DHEA/Cortisol/Aldosterone

Steroid precursor accumulation (defective enzyme function (androstenedione/17aOHprog'one)

Exclude phaeo and neuroblastoma biochemically (metanephrines; NSE); cannot exclude on imaging

Imaging

CT: large>4cm; heterogenous; irregular margins on unenhanced CT; delayed contrast washout

*malignancy increases with size: 2% in <4cm, 6% in 4-6cm, 25% in >6cm

Look for invasion/mets

MRI(T2): large>4cm, heterogenous, irregular margins, delayed gadolinium washout;

*vascular invasion/tumour thrombosis must be excluded before adrenalectomy

[18]FDG PET if lesion/mets/reccurrence can't be imaged on CT/MRI; differentiating benign/malignant lesions, sens100% and spec88%

Staging

*biopsy not recommended (difficult to distinguish between benign and malignant lesion and can cause seeding)

Weiss described 9 histological features (3+ indicates malignant potential)

Ki67 immunohistochemistry may help differentiate benign from malignant disease

TNM staging

Treatment

Surgery is only cure: transabdominal/thoracoabdominal

Medical therapy: mitotane (lipophilic; concentrates in adrenal cortex;induces necrosis by mitchond degeneration)

Tumour response in up to a third

Potentiates cytotoxic activity of some chemo->combinations in advanced disease; results disappointing

Prognosis

Overall 5 year survival 16-38% (depending on stage at diagnosis)

Less than 12 months if mets or non-curative surgery

ADRENOMEDULLARY TUMOURS

Primary: neuroblastoma/phaeochromocytoma/ganglioneuroma
Secondary: common sig of mets (esp breast and bronchial carcinomas)

NEUROBLASTOMA

Highly malignant tumour of sympathetic cells (neuroblasts) in medulla/sympathetic chain
Kids <5 especially
90% sporadic; 10% familial
Site: (i)adrenal (ii)sympathetic chain (neck/chest/pelvis)
Micro: arise from (a)adrenal medullary neuroblasts (b) any neuroectoderm cells along spine
Macro: small nodule → retroperitoneal mass (can undergo haemorrhage/necrosis)
Symptoms: (a) mass (b) bone mets
Biochemistry: Neurone-specific enolase
Imaging: CT/MRI

Treatment:
Surgery followed by chemo/rad ($^{[131]}$MIBG)
Rarely operable but in kids under 12 months can be curative
Resection can lead to regression of mets!

GANGLIONEUROMA

Benign, slow-growing tumour of sympathetic ganglion cells (15% adrenal, 85% sympathetic chain)

PHAEOCHROMOCYTOMA

Physiologically active chromaffin cell tumour in adrenal medulla (neural crest origin) secreting catecholamines (NA)(A) (if extra adrenal in autonomic ganglia = paraganglionoma)
3/million/yr
(a)90% SPORADIC: middle age; very rare in children
(b)10% FAMILIAL (MEN2A/B,VHL,NF1): younger with multiple, bilateral and extra-adrenal tumours
"Rule of 10s: 10% outside adrenals, 10% malignant, 10% bilateral 10% familial"

Genetics

(a)FAMILIAL DISEASE: 3 germline mutations → younger, multiple, bilat, extra-adrenal tumours
1. **RET** (50% of MEN2A/B) 2.**VHL** (third of VHL syndrome) 3.**NF1** (<5% of NF1)
(b) SPORADICs: SDHB/D (succinate dehydrogenase) gene mutations→failure of oxidative phosphorylation
Commonly the underlying mechanism in paraganglionomas

Sites:

90% adrenal; 10% extra-adrenal in autonomic ganglia (sympathetic chain in organ of Zuckerandl)
90% unilateral; 10% bilateral
25% multiple
Also along lower aorta and its bifurcation/urinary bladder/mediastinum etc
Nodes: para-aortic
Mets: bone and liver (8%)

Clinical features:

Caused by paroxysmal secretion of catecholamines -> intermittence is characteristic feature

Symptoms: Headaches/Palpitations/Sweating (postural changes, exercise, anxiety, drugs → provoke symptoms)

Signs: Hypertension/Tachycardia/Sweating

Phaeo crisis: Massive secretion of cats → arrhythmia, sudden death, heart failure, MOF, CVA

Provoked by anaesthesia, ionic contrast, haemorrhage, trauma, biopsy, tumour manipulation at surgery

Biochemical diagnosis

1. 24 hour urinary catecholamines (Plasma catecholamines vary episodically in phaeo so unreliable)

2. Urinary metanephrines

3. **Plasma metanephrines**

**Metanephrines produced continuously by COMT on cats in tumour cells*

**Concentration reflects tumour mass; urinary/plasma metanephrines BOTH near 100% sensitivity/specificity*

**No consensus about whether urinary or plasma free metaphrines are the more accurate measurement*

Imaging:

Only after biochemical confirmation; 5% of adrenal incidentalomas are phaeos

CT: Homogenous mass on unenhanced CT; ionic contrast provokes phaeo crisis (Sensitivity 85-94%)

MRI: Relationship to vascular structures; children and pregnancy(Sensitivity 93-100%)

[18]FDG PET: if CT, MRI etc fail to localise tumour

[131]MIBG combined with SPECT: analogue of NA so taken up by chromaffin cells

Other: Selective venous sampling (IVC and suprarenal veins)

STEP ONE: Medical management

Instituted once diagnosis confirmed: control effects of catecholamines

Alpha blockade before beta blockade: unopposed beta-blockade→hypertensive crisis/pulmonary oedema

Phenoxybenzamine (a-blocker) 20mg BD increasing daily by 10mg until postural hypotension

Period of pre-op blockade: (a)intravascular volume expansion (b)cardiomyopathy improves

Beta-blockade for tachycardia/arrhythmia

STEP TWO: Surgical management:

Adrenalectomy (subtotal may avoid lifelong steroid dependence in patients with multiple, bilateral phaeos)

Tumour removal→ fall in catecholamines → **hypotension and hypoglycaemia** → HDU/ITU post-operatively

Phaeo in pregnancy

Multidisciplinary: obst etrician, paediatrician, endocrinologist, anaesthetist and surgeon

Principles: (i)symptom control (ii)deliver baby (iii)surgically remove tumour

Maternal mortality 30% + significant foetal risk

Clinical features: variable; HTN prominent sign

Diff dx: other pregnangcy-releated forms of HTN

Dx: MRI and metanephrines

(i)Symptom control: alpha blockade +/- beta blockade if persistent tachycardia 10-14 days prior to surgery

(ii)Deliver baby: T3 C-section +/- synchronous adrenalectomy **vaginal delivery contraindicated**

(iii)Remove tumour T1/2= lap adrenalectomy T3= open adrenalectomy synchronous with C-section

ADRENAL INCIDENTALOMA *(European Society of Endocrinology guidelines referenced)*

Tumours inadvertently discovered during investigation of another condition

ESE only recognise lesions >1cm unless signs/symptoms of hormone excess present

Prevalence: third decade; increasing incidence with age; rare in children; 1% of all CTAPs

Classification:

1. **FUNCTIONALITY:** 85% **non-functioning** benign: myolipoma, harmorrhage, adrenocortical cyst, ganglioneuroma, neuroblastoma, lymphoma, CAG, haemangioma, granuloma
   15% **secretory**cortex: adenoma/adenocarcinoma/nodular hyperplasia || medulla: phaeochromocytoma/ganglioneuroma/neuroblastoma
2. **MALIGNANCY:** (i)$ACC_{10\%}$ (ii)$phaeo_{10\%}$ (iii)mets $=_{2.5\%}$ (lung, breast, ovary, kidney, melanoma etc)

Clinical assessment

History: HPc: features of **adrenal secretion** (headache, palpitation, sweating||paraesthesia, cramps||dysmenorrhoea)
FHx: (a)**adrenal disease** and (b)**malignancies** (c)**familial endocrine disease**

Examination: evidence of **cortisol excess**(facial and truncal obesity, plethora, hirsutism, striae)**, virilisation/feminisation**, **hypertension**

Investigations

1 (a)Phaeo: plasma and urinary metanephrines + urinary catecholamines
(b)Cortisol: 24hr urinary free; plasma/salivary midnight cortisol; low-dose overnight dex sup test; ACTH (*ESE:all incidentalomas*)
(c)Mineralocorticoids: (i)PAC and PRA (PAC:PRA>20 = 1^{o} hyperaldosteronism) (ii) urinary aldo/Na+/K+ (iii) electrolytes
(d)Sex Steroids: Serum DHEA/Androstenedione/17a-OHprogesterone (some ACCs/CAH in BAH)
2. Electrolytes: sodium/potassium
3. CXR: lung tumour → ectopic ACTH

*biopsy unhelpful and may provoke phaeochromocytoma crisis

Imaging

CT/MRI aim to detect benign disease; [18F]FDG PET aims to detect malignancy

ESE recommends differentiating between benign/malignant with unenhanced contrast CT

CT (unenhanced)

(a) Benign adenoma: <4cm, homogenous/regular outline/lipid rich or low attenuation **<10 Hounsfield units**

(b)Malignancies: >4cm/irreg outline/heterogenous/lipid poor/high attenuation **>10 Hounsfield units**

MRI:90% distinction between benign/malignant (malignant=higher water content; benign=lipid-rich)

[18F]FDG PET accurately differentiates indeterminate CT/MRI lesions (malignancies tend to have higher uptake than adenomas)

Indeterminate lesions (non-functioning but suspicious appearance on imaging:

1. Immediately re-image w/ other modality 2.Surveillance 6-12 mths - lack of growth imples benign 3. Adrenalectomy

Management

Surgical removal indicated if: 1. Functional tumour 2. Proven/potential malignancy 3. Size 4. Rapid Growth

<4cm (2% ACC): **surveillance** if looks benign *(ESE recommends 6-12 mths with non-contrast CT/MRI)*

4-6cm (6% ACC): **adrenalectomy** or **surveillance**; operate if **rapid growth** (5mm or 20% in 6-12mths) or **looks suspicious**

>6cm (25% ACC): **adrenalectomy** *(ESE recommend laparoscopic if no invasion and unilateral; open if invasive)*

MRI preferable for surveillance due to radiation dose of CT; preferable in all under 40s

Follow-up

Secretory hyperfunction occurs in 9% during follow-up

Bilateral adrenal masses w/ autonomous cortisol secretion, ESE = dealing with autonomous lesion by unilateral adrenalectomy

ESE recommends MDT if: 1. Hypersecretion 2. Suspicious 3. Rapid growth 4. Contemplation of surgery