Cushing's Syndrome

Physiology

↑HPA axis: Hypothalamic CRF → pituitary ACTH → adrenal cortex corticosteroids & androgens.

Cushing's syndrome

ACTH - independent causes

- Iatrogenic exogenous corticosteroids.
- Primary adrenal tumour (adenoma>carcinoma) or hyperplasia
- Carney's syndrome: Cardiac myxoma, freckles and endocrinopathy.
- It can be a feature of multiple endocrine neoplasia, usually MEN1.

Corticotropin (ACTH) - dependent causes

- Excessive amounts of ACTH to stimulate the glands.
    - Cushing's disease - pituitary ACTH-producing tumour (90% microadenomas)
    - Ectopic ACTH production – e.g. lung oat cell Ca., carcinoid
    - Iatrogenic: ACTH administration or its analogues. (uncommon)
- Extra-hypothalamic production of CRF (v.rare)

Clinical features

Obesity or weight gain	Retarded growth in children	Osteopenic fracture
Round (moon) plethoric face	Hypertension	Nephrolithiasis
↓Libido/erectile dysfunction	Depression/emotional lability	Purple abdominal striae
Menstrual irregularity	Impaired glucose tolerance	Water retention
Virilization	Weakness, proximal myopathy	Buffalo hump on neck
Hirsutism, acne	Bitemporal hemianopia (rare)	Supraclavicular fat pad
Thinning of skin, easy bruising	Osteoporosis (dowager's hump)	Clubbing

With ectopic ACTH – Cushingoid features absent, HT+oedema+biochemical features prominent, severe myopathy, cachexia, skin hyperpigmentation.

Differential diagnosis

PCOS, metabolic syndrome X, Obesity, Carney complex, MEN, pseudo-cushing's syndrome, (depression, EtOH or HIV therapy).

Investigations

Urine: 24hr urine for free cortisol.
Bloods: UEC (↓K+), ↑BSL, ABG (met alkalosis), FBC (↑Hct, neutrophilia), cortisol (↑), ACTH (↑↓)
Imaging: CT/MRI head & abdo, CXR for lung Ca
Special: Dexamethasone suppression tests on 24hr-urine & serum cortisol levels – low dose shouldn't suppress cortisol, high dose should suppress in Cushing disease but not ectopic-ACTH. The CRH test can also distinguish these - Cortisol rises only with pituitary disease.

Management

Iatrogenic: Reduction (slowly) of exogenous steroids or use of steroid sparing drugs.
Pituitary adenoma: Surgery or radiotherapy
Adrenal tumours: Surgery (total, partial or bilateral adrenalectomy). Radiotherapy.
Ectopic ACTH production: Surgery if tumour located and not spread. May need medical Rx.

Drug control

Include **mitotane**, **aminoglutethimide**, **metyrapone**, **trilostane** and **ketoconazole**. Metyrapone and ketoconazole tend to suffer "escape" from control and lose effectiveness. Mitotane does not suffer "escape" but is slower to take effect. In ectopic ACTH production, **octreotide** or **lanreotide** may be used, possibly in combination with high dose **cabergoline**.

Prognosis

- Untreated, 50% 5yr mortality. Treated - results are good unless underlying malignancy.
- Poorly controlled Cushing's syndrome is associated with 5x the normal mortality rate.
- Transphenoidal surgery fails in 5% and there is recurrence in 5%.
- If adrenal carcinoma the 5yr survival rate is around 30% even with treatment.
- The prognosis for lung cancer is very poor.

Prevention

- Careful prescription of steroid drugs.
- If high doses and prolonged courses are needed, consider steroid sparing agents.

Hyperaldosteronism

↑Aldosterone → distal renal tubule Na+ retention and K+ excretion → H_2O retention → ↑BP.

Causes

1°hyperaldosteronism (indep. of renin): Adrenal adenoma (Conn's syndrome) 80%, Adrenal hyperplasia, autosomal dominant Glucocorticoid-Remediable Aldosteronism (GRA – ACTH stim production from zona reticularis rather than usual zona glomerula), Adrenal carcinoma (rare).
2° hyperaldosteronism (↑renin): Accelerated phase of hypertension, 1° hyperreninism, 2° to poor perfusion, RAS, coarctation, CCF, nephrotic syndrome, Barrter's, diuretics, liver failure

Presentation

- Hypertension.
- Weakness (from ↓K+), paraesthesiae, lethargy, headache
- Polyuria/polydipsia (reduced ability of the kidneys to concentrate urine)

Investigations

Blood: UEC (↓K+, ↑Na, ABG (met. alkalosis) +), renin (↓ in 1°, ↑ in 2°).
Aldosterone levels: Affected by standing and not suppressible by salt loading (1°). Adrenal venous sampling can identify the involve adrenal/s.
Imaging: CT/MRI abdo for adrenal tumours, renal USS or angiogram if RAS suspected.
Other: ECG.Genetic testing for GRA.

Treatment

Primary hyperaldosteronism

- Conn's syndrome: **spironolactone** followed by surgery.
- Adrenal hyperplasia: **spironolactone** (**SE:** gynaecomastia, menstrual and erectile dysfunction.)
- GRA – steroids e.g. dexamethasone

Secondary hyperaldosteronism: treat under lying cause.

Prognosis

- Prognosis good if 1° hyperaldosteronism but 50 % need life-long antihypertensives.
- Spironolactone probably confers long term benefits in cardiac function