The adrenal glands

The adrenals function as several separate endocrine glands within one anatomical structure.

--The adrenal medulla is an extension of the sympathetic nervous system which secretes catecholamines.

--Most of the adrenal cortex is made up of cells which secrete cortisol and adrenal androgens, and form part of the hypothalamic-pituitary-adrenal axis.

-The small outer glomerulosa of the cortex secretes aldosterone under the control of the renin-angiotensin system..

Subtle alterations in adrenal function may be important in common diseases, including hypertension, obesity and type 2 diabetes mellitus. However, classical syndromes of adrenal hormone deficiency and excess are relatively rare

Glucocorticoids

Cortisol is the major glucocorticoid in humans. Levels are highest in the morning on waking and lowest in the middle of the night.

-Cortisol rises dramatically during stress, including any illness. This elevation protects key metabolic functions (e.g. maintaining cerebral glucose supply during starvation) and puts an important 'brake' on potentially damaging inflammatory responses to infection and injury.

-The clinical importance of cortisol deficiency is, therefore, most obvious at times of stress.

- --In the circulation, more than 95% of cortisol is bound to protein, principally cortisol-binding globulin. It is the free fraction which is biologically active via glucocorticoid receptors.
- --Cortisol can also activate mineralocorticoid receptors, but it does not normally do so because most cells containing mineralocorticoid receptors also express an enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts cortisol to its inactive metabolite, cortisone.
- --Loss of this protection of mineralocorticoid receptors by inhibition of 11β-HSD2 (e.g. by liquorice) results in cortisol acting like aldosterone as a potent sodium-retaining steroid

Mineralocorticoids

Aldosterone is the body's most important sodium-retaining hormone, acting via mineralocorticoid receptors. Sodium is retained at the expense of increased excretion of potassium. Increased potassium in the lumen of the distal nephron also results in increased exchange with protons and metabolic alkalosis.

--The principal stimulus to aldosterone secretion is angiotensin II, a peptide produced by activation of the renin-angiotensin system .

- Renin secretion from the juxtaglomerular apparatus in the kidney is stimulated by low perfusion pressure in the afferent arteriole,.

- --As a result, renin is increased in hypovolaemia and renal artery stenosis, and renin concentrations when standing are about double those when lying down

Catecholamines

In humans, only a small proportion of circulating noradrenaline (norepinephrine) is derived from the adrenal medulla; much more is released from other nerve endings.

-The methyltransferase enzyme responsible for the conversion of noradrenaline to adrenaline (epinephrine) is induced by glucocorticoids.

-- Blood flow in the adrenal is centripetal so that the medulla is bathed in high concentrations of cortisol ------so it is the major source of circulating adrenaline.

Adrenal androgens

are secreted in response to ACTH and are the most abundant steroids in the blood stream.

--They are probably important in the initiation of puberty (the adrenarche).

-- The adrenals are also the major source of androgens in adult females and may be important in female libido

CUSHING'S SYNDROME

Cushing's syndrome is caused by excessive activation of glucocorticoid receptors.

--By far the most common cause is iatrogenic, due to prolonged administration of synthetic glucocorticoids such as prednisolone.

- Non-iatrogenic Cushing's syndrome is rare, although it presents by many diverse routes and is often a 'spot diagnosis'.

Aetiolog

Amongst endogenous causes, pituitary-dependent cortisol excess (by convention, called Cushing's disease) accounts for ~80% of cases.

--Both Cushing's disease and adrenal tumour are four times more common in women than men.

-In contrast, ectopic ACTH syndrome (often due to a small-cell carcinoma of the bronchus) is more common in men

the Causes of Cushing's syndrome

---**ACTH-dependent**

--Pituitary adenoma secreting ACTH (i.e. Cushing's disease--)

--Ectopic ACTH syndrome (e.g. bronchial carcinoid, small-cell lung carcinoma, pancreatic neuro-endocrine tumour)

-- latrogenic (ACTH therapy--)

---**Non-ACTH-dependent**

Iatrogenic (chronic glucocorticoid therapy, e.g. for asthma--)

---Adrenal adenoma

---Adrenal carcinoma

---**Pseudo-Cushing's syndrome**, i.e. cortisol excess as part of another illness

--- Alcohol excess (biochemical and clinical features)

---Major depressive illness (biochemical features only, some clinical overlap, --)

---Primary obesity (mild biochemical features, some clinical overlap

Clinical assessment

Many of manifestations of glucocorticoid excess are not specific to Cushing's syndrome

--. Moreover, some common disorders can be confused with Cushing's syndrome because they are associated with alterations in cortisol secretion: for example, obesity and depression. Features which have the best predictive value in favour of Cushing's syndrome in an obese patient are bruising, myopathy and hypertension. Any clinical suspicion of cortisol excess is best resolved by further investigation.

-- In all patients with features of Cushing's syndrome it is vital to exclude iatrogenic causes. Even inhaled or topical glucocorticoid administration can induce Cushing's syndrome in susceptible individuals. A careful drug history must be taken before embarking on complex investigations.

- Some clinical features are more common in ectopic ACTH syndrome. Unlike pituitary tumours secreting ACTH, ectopic tumours have no residual negative feedback sensitivity to cortisol, and both ACTH and cortisol levels are usually higher than with other causes.
- --Very high ACTH levels are associated with marked pigmentation.
- --Very high cortisol levels overcome the barrier of 11β-HSD2 in the kidney and cause hypokalaemic alkalosis. Hypokalaemia aggravates both myopathy and hyperglycaemia (by inhibiting insulin secretion).

-When the tumour secreting ACTH is malignant (e.g. small-cell lung carcinoma), then the onset is usually rapid and may be associated with cachexia.

-For these reasons, the classical features of Cushing's syndrome are less common in ectopic ACTH syndrome, and if present suggest that a less aggressive tumour (e.g. bronchial carcinoid) is responsible.

-In Cushing's disease, the pituitary tumour is usually a microadenoma (< 10 mm in diameter); hence other features of a pituitary macroadenoma (hypopituitarism, visual failure or disconnection hyperprolactinaemia are rare

Investigations

The large number of tests available for Cushing's syndrome reflects the fact that no single test is infallible and several are needed to establish the diagnosis.

-it is useful to divide investigations into those which establish whether the patient has Cushing's syndrome, and those which are used subsequently to elucidate the aetiology .

--**Does the patient have Cushing's syndrome??**

- Plasma cortisol levels are highly variable in healthy subjects so that patients with Cushing's syndrome often have daytime values within the normal range. For this reason, there is no place for a random measurement of daytime plasma cortisol in the clinic in either supporting or refuting the diagnosis.

--Cushing's syndrome is confirmed by the demonstration of increased secretion of cortisol (measured in urine) that fails to suppress with relatively low doses of dexamethasone (measured in plasma or urine).

--Loss of diurnal variation, with elevated evening plasma cortisol, is also characteristic of Cushing's syndrome, but samples are awkward to obtain

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--Dexamethasone is used for suppression testing because, unlike prednisolone, it does not cross-react in radioimmunoassays for cortisol.

--. Also, the hypothalamic-pituitary-adrenal axis may 'escape' from suppression by dexamethasone if a more potent influence such as psychological stress supervenes.

- There is a rare syndrome of cyclical Cushing's syndrome in which the excessive secretion of cortisol is episodic. If there is a strong clinical suspicion of Cushing's syndrome but initial screening tests are normal, then weekly 24-hour urine cortisol measurements for up to 3 months are sometimes justified

What is the cause of the Cushing's syndrome??

-- Once the presence of Cushing's syndrome is confirmed, measurement of plasma ACTH is the key to establishing the differential diagnosis.

- In the presence of excess cortisol secretion, an undetectable ACTH indicates an adrenal tumour, while any detectable ACTH is pathological.

--Tests to discriminate pituitary from ectopic sources of ACTH rely on the fact that pituitary tumours, but not ectopic tumours, retain some features of normal regulation of ACTH secretion. Thus, in Cushing's disease ACTH secretion is suppressed by dexamethasone, at a higher dose than in health, and ACTH is stimulated by corticotrophin-releasing hormone (CRH).

- --localisation of tumours secreting ACTH or cortisol by MRI with gadolinium contrast enhancement detects around 70% of pituitary microadenomas secreting ACTH.
- --Venous catheterisation with measurement of inferior petrosal sinus ACTH (i.e. draining directly from the pituitary) may be helpful in confirming Cushing's disease if the MRI does not show a microadenoma.
- - CT or MRI detects most adrenal adenomas. Adrenal carcinomas are usually large (> 5 cm).

TESTS FOR CUSHING'S SYNDROME

Test

Protocol

1 -does the patient have Cushing's syndrome?

A-Overnight dexamethasone suppression test

1 mg orally at midnight;

measure plasma cortisol at 0800-0900 hrs

Plasma cortisol < 60 nmol/l (< 2.2 µg/dl) excludes Cushing's

B- Low-dose dexamethasone suppression test

0.5 mg 6-hourly for 48 hrs;

sample 24-hr urine cortisol during second day and 0900-hr plasma cortisol after 48 hrs

Urine cortisol < 100 nmol/day (36 µg/day) or plasma cortisol < 60 nmol/l (< 2.2 µg/dl) excludes Cushing's

2-what is the cause of crushing's syndrome

A-High-dose dexamethasone suppression test==

2 mg 6-hourly for 48 hrs;

sample 24-hr urine cortisol at baseline and during second day

Urine cortisol < 50% of basal suggests pituitary-dependent Adisease;
> 50% of basal suggests ectopic ACTH syndrome

B-Corticotrophin-releasing hormone test

100 µg ovine CRH i.v. and monitor plasma ACTH and cortisol for 2 hr

Peak plasma cortisol > 120% and/or ACTH > 150% of basal values suggests pituitary-dependent disease; lesser responses suggest ectopic ACTH syndrome

C- Inferior petrosal sinus sampling

Catheters placed in both inferior petrosal sinuses and simultaneous sampling from these and peripheral blood for ACTH; may be repeated 10 minutes after peripheral CRH injection

ACTH concentration in either petrosal sinus > 200% peripheral ACTH suggests pituitary-dependent disease; < 150% suggests ectopic ACTH syndrome

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Management

--Untreated Cushing's syndrome has a 50% 5-year mortality.

--Most patients are treated surgically with medical therapy given for a few weeks prior to operation.

--A number of drugs are used to inhibit corticosteroid biosynthesis, including metyrapone, aminoglutethimide and ketoconazole. The dose of these agents is best titrated against 24-hour urine free cortisol

--Cushing's disease

Trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice. Experienced surgeons can identify microadenomas which were not detected by MRI and cure about 80% of patients.

- If the operation is unsuccessful then bilateral adrenalectomy is an alternative.

-If bilateral adrenalectomy is used in patients with pituitary-dependent Cushing's syndrome, then there is a risk that the pituitary tumour will grow in the absence of the negative feedback suppression previously provided by elevated cortisol levels. This can result in Nelson's syndrome, with an aggressive pituitary macroadenoma and very high ACTH levels causing pigmentation. Nelson's syndrome can be prevented by pituitary irradiation

--Adrenal tumours

Adrenal adenomas are removed via laparoscopy or a loin incision. Adrenal carcinomas are resected if possible,

- the tumour bed irradiated and the patient given the adrenolytic drug mitotane.

-Cytotoxic chemotherapy may retard disease progression in patients with metastases.

--Ectopic ACTH syndrome

Localised tumours causing this syndrome (e.g. bronchial carcinoid) should be removed.

-During treatment or palliation of non-resectable malignancies, it is important to reduce the severity of the Cushing's syndrome using medical therapy