THE ADRENAL GLAND

Anatomy:
Lie along the anteromedial border of the superior pole of the kidney. Each consists of an inner medulla (28%) which secretes nor-epinephrine & dopamine & an outer cortex which is divided into 3 zones:
Zona glomerulosa 15% → Aldosterone (mineralocorticoid)
Zona fasciculate 50% → cortisol (glucocorticoid)
Zona reticularis 7% → androgens

ACTH has a diurnal pattern of secretion so that cortisol levels are highest in the morning on waking & lowest in the middle of the night.

The major pathways of synthesis of steroid hormones. (DHEA = dehydroepiandrosterone; OHase = hydroxylase; HSD = hydroxysteroid dehydrogenase)
Physiology

Physiologic effects of Glucocorticoids are:

1. Effects on intermediary metabolism
   - $\uparrow$ protein catabolism
   - $\uparrow$ hepatic glycogenesis & gluconeogenesis, glucose 6 phosphate activity $\uparrow$ & the blood glucose level rises. Cortisol exerts anti-insulin effect in peripheral tissues & makes diabetes worse.

2. Permissive action: That are metabolic reactions produced by other hormones through effect of glucocorticoids but not directly through it e.g: calorigenic effects of glucagons & catecholamine, lipolytic effect & bronchodilation effects of catecholamine.

3. Effects on ACTH secretion

4. Vascular reactivity: Glucocorticoid exerts these vascular effects through nor epinephrine.

5. Effects on N.S (euphoria or psychological illness may occur).


7. Effects on blood cells & lymphatic organs.
   - $\downarrow$ No of eosinophils, by $\uparrow$ their sequestration in spleen & lungs
   - $\downarrow$ No of basophils.
   - $\downarrow$ circulating lymphocytes count & size of lymphnodes & thymus by inhibiting lymphocyte mitotic activity (primary effect by inhibition of IL-2 which is produced by T-lymphocytes, thus cortisol impairs CMI).
   - $\uparrow$ No of neutrophils, platelets & RBC.


9. Effects on calcium metabolism (reduction of hypercalcemia)

10. Glucocorticoids $\uparrow$ the intraocular pressure, they can precipitate glaucoma in susceptible individuals & can enhance cataract formation.

11. Effects on G.I.T (delayed healing of peptic ulcer)

12. In excess, glucocorticoids inhibit linear growth.
CUSHING’S SYNDROME

It’s the symptoms & signs associated with prolonged inappropriate elevation of free corticosteroid levels. In 1932 Harvey Cushing ascribed the syndrome to a basophilic adenoma of the anterior pituitary. Cushing’s syndrome is caused by excessive activation of glucocorticoid receptors. By far the most common cause is iatrogenic, due to prolong administration of synthetic glucocorticoid such as prednisolone.

Classification

<table>
<thead>
<tr>
<th>ACTH-dependent</th>
<th>Non-ACTH-dependent</th>
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<tbody>
<tr>
<td>Iatrogenic ACTH therapy</td>
<td>Iatrogenic (e.g: prednisolone)</td>
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<tr>
<td>Pituitary-dependent bilateral</td>
<td>Adrenal adenoma</td>
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<tr>
<td>Adrenal hyperplasia (Cushing’s disease)</td>
<td>Adrenal carcinoma</td>
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<tr>
<td>Ectopic ACTH syndrome (benign or malignant non-endocrine tumour)</td>
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Cushing’s disease & adrenal tumor 4 times more common in ♀ while ectopic ACTH syndrome (often due to a small cell ca. of bronchus) more common in ♂.

Clinical features

1. Weight gain 91%, obesity (centripetal) 97%, hirsutism.
2. Bruising, striae (livid stretch marks specially over the abdomen, buttock & thighs), plethoric appearance, moon-face, back pain (from compression & they may exuberant callus with #, osteoporosis), proximal myopathy.
3. Impaired glucose tolerance due to ↑ gluconeogenesis, sever hypokalaemic alkalosis, skin pigmentation & these are much more common in ectopic ACTH syndrome.
4. Skin infection especially with fungi.
5. Poorly skin healing.
7. Hypertension is common.
8. Oligomenorrhea or amenorrhea in women & impotence in men.

Differential diagnosis

1. Pseudo cushing’s syndrome.
2. Exogenous obesity (mild biochemical features, some clinical overlap).
3. Chronic alcoholism (biochemical & clinical features).
4. Major depressive illness (biochemical feature only some clinical overlap)

Investigations

In iatrogenic cushing’s syndrome, cortisol levels are low unless the patient is taking a corticosteroid (such as prednisolone) which cross – reacts in immunoassays with cortisol.

1. Diagnosis: does the patient have C.S?
2. DD: what is the cause of the adrenocortical hyperfunction?
Does the patient have Cushing's syndrome?

1. Loss of circadian rhythm of plasma cortisol this may also be lost by stress caused from hospital admission, depression or HF.

2. Overnight dexamethasone suppression test by giving 1 mg orally dexamethasone at midnight & to measure plasma cortisol next day at 09:00 plasma cortisol<60nmol/L excludes cushing's.

3. Elevated 24 hours urinary free cortisol.

4. Insulin induced hypoglycemia in which there is no rise in plasma cortisol in patient with C.S it’s the only test which distinguishes patients with severe depression from those with C.S.

What is the cause of Cushing’s syndrome?

Plasma ACTH at 8:00 a.m

Very high levels above (300 ng/l) suggest the ectopic ACTH typically in pts. With Ca bronchus. Levels within the normal range (10-80 ng/l) usually indicates a pituitary source.

Values between (80-300ng/l) may relate to either pituitary dependent disease or the ectopic ACTH syndrome (usually from benign source such as bronchial carcinoid). While ACTH level will be undetectable in adrenal tumors.

High dose dexamethasone test by using 2 mg dexamethasone 6 hourly for 48 hr. & to measure plasma cortisol after 48 hr. in which it will be suppressible in pituitary dependent cushing's disease while not suppressible in ectopic ACTH & adrenal tumor.

Also measurement of plasma K will be helpful in which it will be low less than 3.5 mmole /L in ectopic ACTH & normal in others.

*Techniques for localizing of tumor secreting ACTH or cortisol are:

*Pituitary source :MRI of pituitary; it detects about 70% of pituitary microadenomas secreting ACTH

*Ectopic source are : chest x-ray, CT chest & abdomen, tumor markers + /- multiple venous sampling for ACTH

*Adrenal cause: CT adrenals +/- adrenal vein sampling

Treatment

Treatment of choice depends on the cause:

1. Cushing’s disease:

Tras-sphenoidal surgery with cure rate of 80% is the treatment of choice. After surgery the cells around adenoma are suppressed so dexamethasone 0.5 mg morning given & measure plasma cortisol 2 weekly interval if >180 nmole /L stop dexamethasone, this recovery takes up to 18 months.

When tumor is not found & the diagnosis is definitely cushing’s disease the radical hypophysectomy may be required. If the diagnosis is not certain then bilateral adrenalectomy with pituitary irradiation to prevent the diagnosis of Nelson’s syndrome may be the correct treatment.

Other way of treatment is interstitial irradiation by Yttrium 90. External pituitary irradiation is of little value in adult but effective in children.
2. **Ectopic ACTH syndrome:**

Surgical for benign tumors e.g: Bronchial carcinoid. For malignancy as in ca. bronchus initially may respond to chemotherapy or radiotherapy & drug as metyrapone, aminogluthethemide, may be useful.

Medical therapy:

- Cyproheptadin.
- Ketoconazole (600-1200mg/day).
- Mitotane (2-3 gm/day).
- Metyrapone (2-3 gm/day).

3. **Nelson’s syndrome:**

Is the association of locally invasive pituitary tumor with very high level of ACTH with hyper pigmentation which may occur in some pts. With cushing’s disease following bilateral adrenalectomy.

It should not occur if pituitary irradiation done with bilateral adrenalectomy, if it occur surgery, radiotherapy & drugs as γaminobutyric acid inhibitor, sodium valproate may all be necessary but are often ineffective.

Prognosis: Unrelated cushing’s syndrome has 50% five year mortality.

4. **Adrenal tumor:**

Adrenal adenomas should be surgically removed with laparoscopy or loin incision. It may take several months for the contralateral adrenal & the hypothalamus & pituitary to recover from suppression. During this time sub optimal replacement therapy is required (0.5 mg dexamethasone in the morning).

Adrenal Ca should also be removed if possible, the tumor bed irradiated & the pt. given adrenolytic drug like O’,P.’DDD. This may produce nausea & ataxia. Dexamethasone is used for suppression testing because unlike prednesolone it does not cross-react in radioimmunoassay for cortisol.
ADRENOCORTICAL INSUFFICIENCY

Can be divided into primary & secondary causes:

Primary includes:
1. Addison’s disease .
2. Congenital or acquired enzyme defects .

Secondary includes:
1. Hypothalamic or pituitary disease .
2. Glucocorticoid therapy.

ADDISON’S DISEASE

It’s rare condition in the developed world .In 1855 Addison’s described the disease .

Causes of Addison’s disease:

Common cause:
Autoimmune more in ♀ than in ♂ (2:1) . may be sporadic or poly glandular deficiency type I (includes Addison’s disease , chronic mucocutaneous candidiasis , hypoparathyroidism ).or poly glandular deficiency type II (includes Addison’s disease ,primary hypothyroidism , primary hypogonadism , IDDM , pernicious anemia ,vitiligo). Other common causes are T.B & bilateral adrenalectomy .

Rare causes:
Metastatic tumor , lymphoma , intra -adrenal hemorrhage (waterhouse-Friedrichsen syndrome following meningococcal septicemia) ,amyloid, haemochromatosis , adrenal infarction or infection other than T.B (especially AIDS).

Clinical features:
Includes those due to both glucocorticoid & mineralocorticoid insufficiency with loss of adrenal androgen production & ↑ ACTH secretion .They may present with acute , chronic or acute on chronic illness .

Glucocorticoid insufficiency will cause wt. loss , malaise weakness ,anorexia ,nausea, vomiting ,diarrhea, or constipation , postural hypotension which is almost invariably present, hypoglycemia. Mineralocorticoid insufficiency lead to hypotension.

↑ACTH secretion cause pigmentation in sun exposed areas , pressure areas e.g: elbows , knees ,palmer creases ,knuckles , mucous membrane ,conjunctiva ,recent scars . Loss of adrenal androgens cause ↓ body hair especially in ♀ .Vitiligo is present in 10-20% .surgery or other stress may precipitate an acute adrenal crisis.

Investigations:
Plasma electrolyte :especially in gradual adrenal destruction there will be ↓ Na ,↑ K ,plasma urea ↑ there will be neutropenia, eosinophilia , & a relative lymphocytosis , there will be low blood glucose especially in sever adrenal insufficiency .

ACTH stimulation test: Basal at 08:00h plasma cortisol is low or normal (low for seriously ill pt.),so(synacthen) 0.25 mg I.M given it is biologically active .ACTH (24 out of 39 aminoacid) plasma cortisol at 0.30 & 60 minutes is measured, normally plasma cortisol should exceed 550 nmole /L, in primary adrenal insufficiency there will be no rise.
in secondary adrenal insufficiency may also get sub normal cortisol rise so either ACTH measurement or depot synacthen 1mg I.M for 3 days is used after 8 hours from the last injection measure cortisol level it will be less than 700 nmole /l in primary while there will be progressive cortisol rise in secondary adrenal insufficiency.

**Plasma ACTH:**

Primary adrenal insufficiency ↑ ACTH.

Secondary adrenal insufficiency ↓ ACTH.

Even if plasma cortisol is normal in primary adrenal insufficiency. Plasma rennin activity are nearly always high. Aldosterone either low or normal.

**Other investigation to find the cause by:**

CXR ,plain X-ray ,or CT scan of abdomen for calcification.

Blood exam. For adrenal or organ specific antibody , associated thyroid disease , D.M.

**Management:**

Both glucocorticoid & mineralocorticoid should be given.

Cortisol (hydrocortisone ) 20 mg morning & 10 mg at 18:00 hour .Or cortisone acetate 25 mg morning and 12.5 mg evening for glucocorticoid replacement

Fludrocortisone 0.05-0.1 mg/day for mineralocorticoid replacement.

Adequacy of therapy measured by body wt, B.P, plasma electrolyte & plasma renin activity. T.B. should be treated.

**Adrenal Crisis**

Patients may present in shock with sever hypotension , hyponatremia, hypercalemia and in some instances , hypoglycemia.Muscle cramps , nausea ,vomiting , diarrhea ,and unexplained fever may be present. Intercurrent disease or infection may be the precipitating cause. The adrenal crisis is a medical emergency & requires I.V hydrocortisone hemisuccinate 100mg & I.V fluid ( normal saline &5% dextrose if hypoglycemic ).parentral hydrocortisone should be continued (100 mg I.M hourly )until the gastro intestinal symptoms abate before starting oral therapy .The precipitating cause should be sought & if possible treated.

**Advices to patients with adrenal insufficiency:**

1. The pt. must have steroid card,
2. During intercurrent stress e.g: febrile illness , double the dose of hydrocortisone .
3. During minor operation 100mg hydrocortisone by I.M with premedication must be given .for major operation hydrocortisone 100mg every 6 hour for 24 hours later on 50 mg I.m every 6 hourly should be given .
4. If Addison’s disease has gastroenteritis, cortisol replacement must be changed to parentral hydrocortisone if unable to take it by mouth.
MINERALOCORTICOID EXCESS:

Aldosterone production is under the control of angiotensin II. ACTH & hyperkalaemia are less important stimuli. low salt intake also stimulates aldosterone secretion.

Hyperaldosteronism may be primary or secondary. Primary hyperaldosteronism: (Conn’s syndrome). There is primary abnormality in the zona glomerulosa either by an adenoma in (60%) of the cases or bilateral zona glomerulosa hyperplasia (may be either idiopathic or ACTH dependent)

C/F

Hypertension & hypokalaemia will lead to muscle weakness tetany because of the metabolic alkalosis with low ca++ & poly urea , polydipsia , secondary to renal tubular damage (nephrogenic diabetes insipidus) , diuretic therapy mainly thiazide may leads to marked hypokalemia. Conn’s syndrome is rare cause of H.T (1%) & more common in negroids.

Investigations

1. Plasma K: it should be measured several times & pt. on normal salt intake without diuretic ,blood should be taken without occlusion or muscular exercise of the arm , & avoid hemolysis by rapid sample separation ,if still there is low K , so:

2. Plasma or urinary aldosterone & plasma rennin activity done, it is better to stop antihypertensive drug.

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
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<tr>
<td>Aldosterone</td>
<td>↑ ↑</td>
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<tr>
<td>PRA</td>
<td>suppressed ↑</td>
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To differentiate between the causes of primary hyperaldosteronism several investigations can be helpful as: aldosterone response to posture, adrenal vein catheter , dexamethasone suppression , the measurement of 18-OH cortisol & adrenal scan with selenium 75 cholesterol which will demonstrate adenoma.
Management:

Spironolactone which is aldosterone antagonist up to 400mg/day may be required, the response correlates with the response of removal of an adenoma surgically by unilateral adrenalectomy.

Idiopathic hyperplasia may respond to spironolactone also. 20% of male develops gynaecomastia so amiloride 10-40 mg/day can be substituted some time captopril are often of value.

SECONDARY HYPERALDOSTERONISM:

This is a very common clinical problem resulting from excessive activity of the rennin – angiotensin system.

Causes:

Physiological: as in case of salt depletion by inadequate intake or by excessive loss from kidney or G.I.T, some time it may occur in pregnancy.

Pathological: nephrotic syndrome, cirrhosis with ascites & congestive heart failure, Bartter’s syndrome usually also have short stature, hypokalemia, high rennin, less marked hyperaldosteronism, hyperplasia of the juxta glomerular apparatus & ↑ urinary prostaglandin excretion.

Accelerated or malignant H.T, severe renal artery stenosis

Rennin secreting tumor (haemangiopericytoma) are very rare. Excessive diuretic therapy is the commonest cause.

Investigation:

1. there is hypokalemia & plasma Na level in the lower part of the reference range or subnormal.
2. ↑ plasma aldosterone & plasma rennin.

Treatment:

Treatment of underlying cause e.g: for salt depletion give I.V saline. In congestive heart failure either spironolactone or captopril in Bartter’s syndrome usually also have short stature, hypokalemia, high rennin, less marked hyperaldosteronism, hyperplasia of the juxta glomerular apparatus & ↑ urinary prostaglandin excretion. if the cause is due to excessive diuretic therapy e.g: with a thiazide with hypokalemia then give a K sparing drug such as amiloride, triamterene or spironolactone.

PHAEOMOCYTOMA:

This is a rare tumor of chromaffin tissue which secretes catecholamines & is responsible for less than 0.1% of causes of H.T. The tumors are usually benign 10% malignant in over 90% of cases the tumor found in the adrenal medulla. There is a useful rule of tens’ in this condition:

10% are malignant.
10% are extraadrenal.
10% are familial.

It is associated with MEN type II.

C/F:

These depend on the catecholamine secretion, the C/F include:
Hypertension (usually paroxysmal) (often postural drop of B.P), some pt. may present with a complication of the hypertension e.g: stroke, MI, LVF. Occasionally the pt. may be hypotensive (specially dopamine – secreting tumors).

During the attack the pt. presents with: pallor (some time flushing), palpitation, sweating, headache, anxiety (feeling of death).

There may be abdominal pain with vomiting, constipation, wt. loss, glucose intolerance, neurofibromatosis is associated with an ↑ incidence of phaeochromocytoma.

Investigation:

Excessive secretion of catecholamines can be confirmed by measuring the hormones (adrenalin, nore adrenalin & dopamine) in plasma or their metabolites (e.g: Vallinyl mandelic acid VMA) in urine, however catecholamine secretion is usually paroxysmal, so that measurement in a 24 hr. urine collection are more useful than single measurement for screening. Increased urinary catecholamine excretion occurs in stressed patients (e.g: after MI or major surgery) & is induced by some drugs (β –blocker & antidepressant) for this reason a suppression test may be valuable e.g:plasma catecholamine 10 minutes after 2.5 mg I.V pentolinum, in normal subject levels will suppress unlike those with phaeochromocytoma.

Once the diagnosis made, the tumor must be localized by:
CT scanning
Scintigraphy using meta-iodobenzyl guanidine(MIBG).
If the tumor can not be localized then selective venous sampling with measurement of plasma nore adrenalin may be required.

Management

This requires excision of the tumor or long term TX with α and (usually β) adrenoceptor blockade.

Prior to surgery give α –antagonist drug such as phenoxybenzamine 10-20 mg orally 3-4 times / day for a minimum of 6 weeks to allow restoration of normal plasma volume if tachycardia is there then β –antagonist as propranolol (10-20 mg) 3 times daily should be added.

β-antagonist should not be given before the α-antagonist.

During surgery Na-nitropruside & the short acting α-antagonist phentolamine are very useful in controlling hypertension episodes which may occur during anaesthesia or mobilization of the tumor.