ADRENAL INSUFFICIENCY

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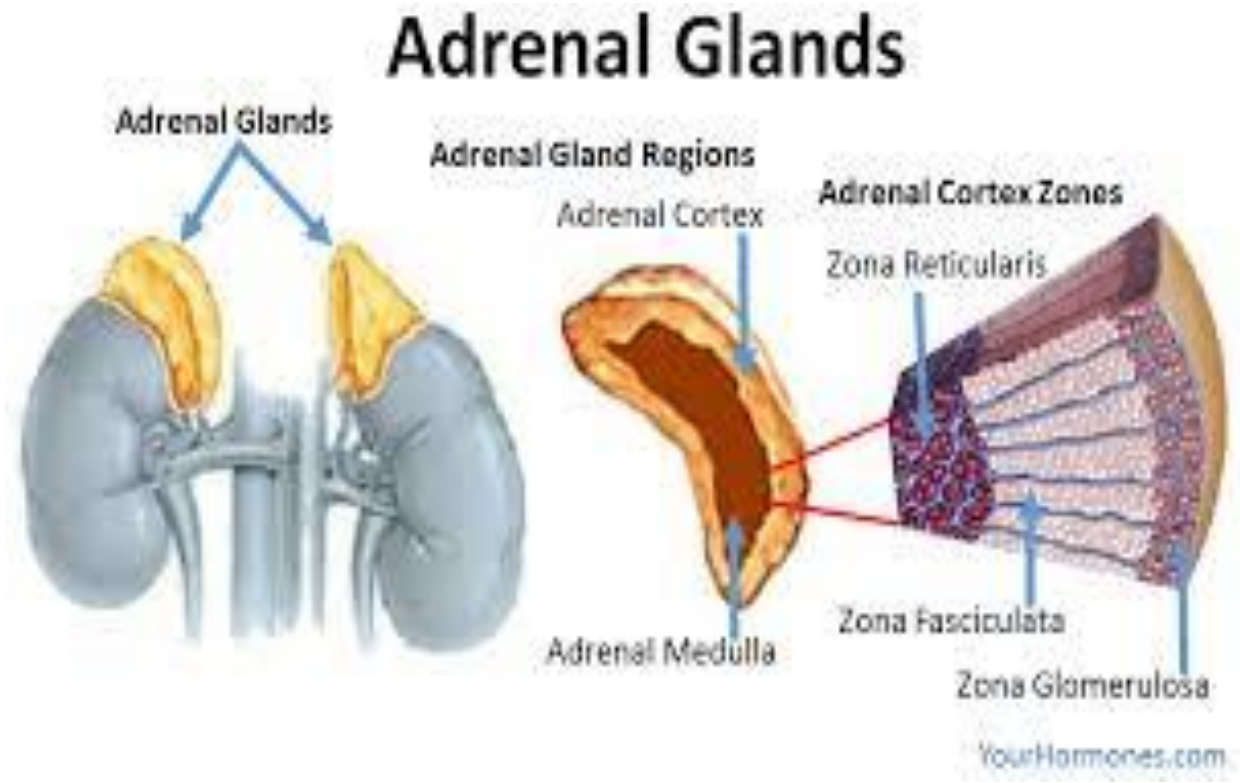
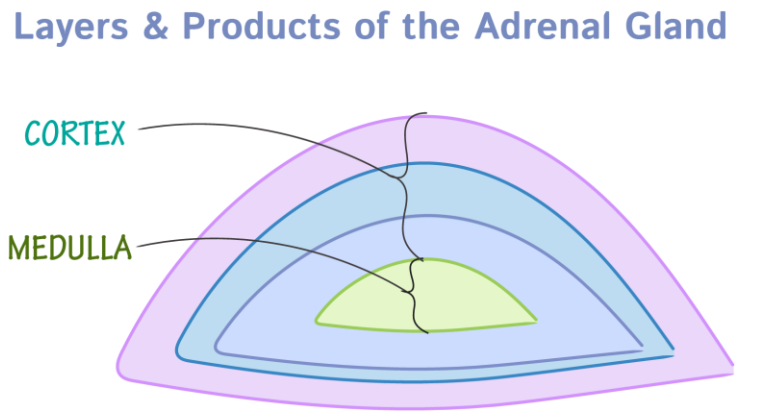
18 AUGUST 2021

Anatomy & Physiology of Adrenal Glands





CORTEX
Zona glomerulosa — Mineralocorticoids
Zona fasciculata — Glucocorticoids
Zona reticularis — Androgens
MEDULLA
Catecholamines

Dimension: 5cm (L) x3cm (W) x1cm (D)

Adrenal Pathologies

Excessive secretion

– Cushing's Syndrome, Primary Aldosteronism, Phaeochromocytoma

Tumour/Incidentaloma

– Adrenal adenoma/carcinoma

Genetic disorder (e.g. 21 hydroxylase deficiency)

– Congenital Adrenal Hyperplasia

Insufficiency

– Addison's disease (primary adrenal insufficiency)

- Secondary / Tertiary adrenal insufficiency

Case One

16 y/o girl

Graves' disease diagnosed 3 years ago (proptosis, oligomenorrhoea, unable to gain weight)

- treated, now off Carbimazole

New issue: chest keloid, recent courses of intralesional triamcinolone, so far received 4 treatment (either 40mg/ml or 10mg/ml dose), 4-6 weeks apart.

Mum noted "moon face"

8am cortisol tested and it is low <14 nmol/L (normal 150-540)

Questions:

1. diagnosis

2. management

Adrenal Insufficiency (AI)

- Onset often gradual

- May go undetected until illness or stress precipitated adrenal crisis

Causes of adrenal insufficiency:

1. Primary (Addison's disease) – **autoimmune**, TB, HIV, fungal, lymphoma, metastasis, haemorrhage

2. Secondary – **hypopituitarism**, pituitary apoplexy, autoimmune isolated ACTH deficiency (rare)

3. Tertiary – **chronic high dose steroid**, cure of Cushing's syndrome

Acute adrenal Insufficiency- Adrenal Crisis

Shock

Anorexia

Vomiting

Abdominal pain

Lethargy/lassitude

Fever

Confusion

Coma

Acute Adrenal Insufficiency - clinical setting/precipitating factors

- Serious infection
- Major stress/surgery/trauma/burn
- Adrenal infarction, haemorrhage, injury, emboli
- Pituitary infarction or haemorrhage
- Under replaced glucocorticoid or mineralocorticoid
- Fail to take more glucocorticoid during illness
- Persisting vomiting or diarrhoea
- Abrupt withdrawal of high dose of glucocorticoid

Chronic primary Adrenal Insufficiency

May have symptoms of glucocorticoid, mineralocorticoid and androgen (women) deficiency

Onset if often insidious and gradual. Diagnosis is often difficult in early stage

Common clinical features:

1. Fatigue (84-95%)
2. Weight loss (66-76%) – anorexia, dehydration
3. Nausea, vomiting, abdominal pain (50-60%)
4. Diffuse myalgia and arthralgia (35-40%)
5. **Skin hyperpigmentation (**40-75%)
6. Postural hypotension (55-68%)
7. Salt craving (38-64%)
8. Decrease axillary & pubic hair, loss of libido (women)

9 Psychiatry (memory loss, psychosis, depression, mania)

Hyperpigmentation in chronic AI

- Most characteristic physical sign

- Consequence of cortisol deficiency

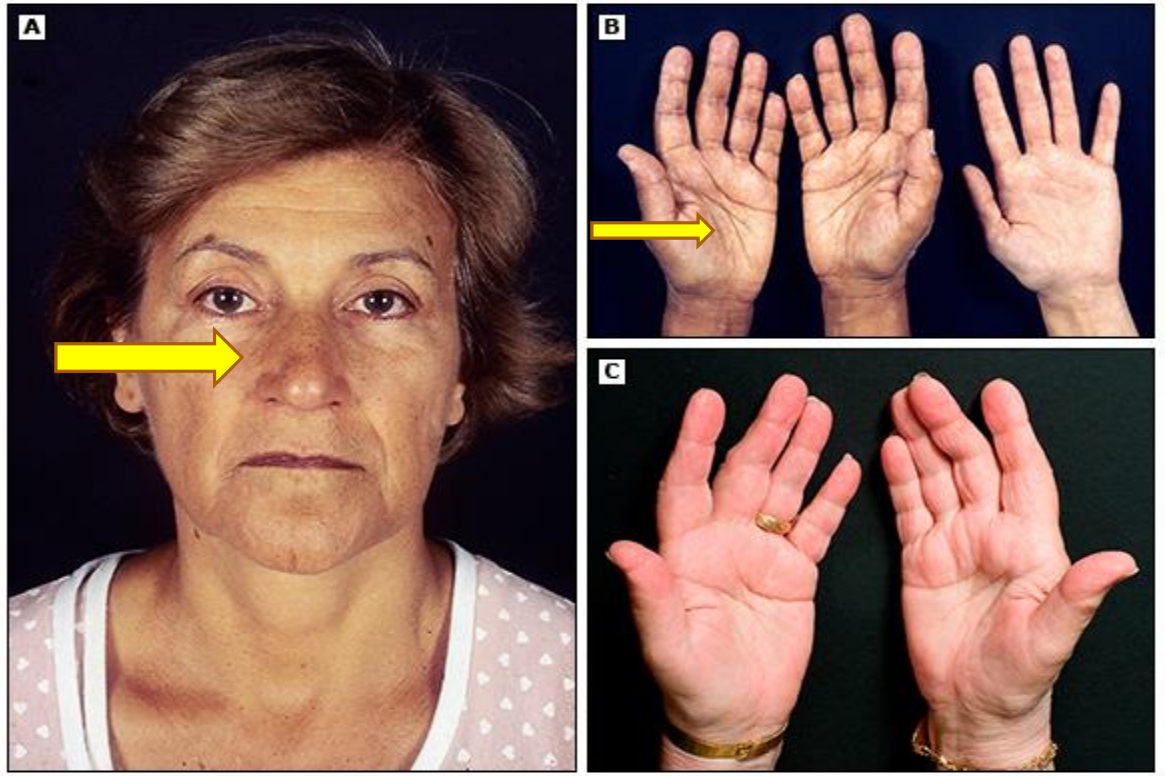
- Increased POMC, MSH and melanin

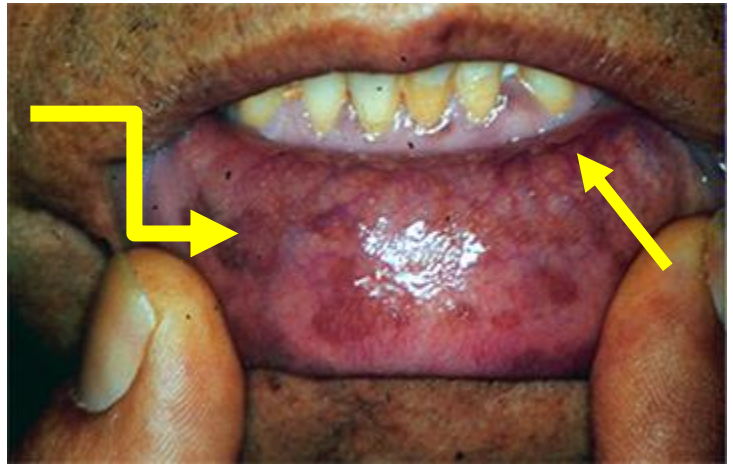
- Generalised pattern

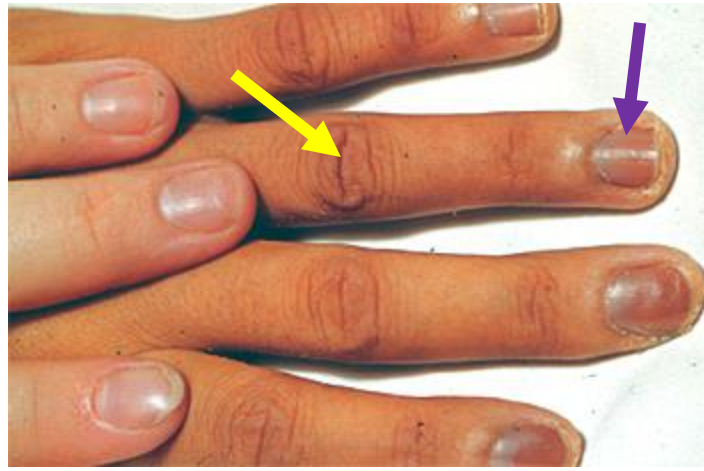
- Most conspicuous on sun exposed areas

(face, neck, back of hands) & areas exposed to friction (elbow, knee, spine, knuckles),

palmar crease, areola, axilla, umbilicus







Chronic Primary Adrenal Insufficiency - lab findings

- Hyponatremia (70-80%) – Na loss (↓tubular Na reabsorption), volume depletion
- Hyperkalemia
- Mild hyperchloreamic acidosis (~40%) – mineralocorticoid deficiency (↓ H+ secretion)
- Hypercalcemia (rare, maybe a/w AKI)
- **Hypoglycaemia (rare in acute AI)**
- Normochromic anaemia (+/- pernicious anaemia)

Treatment of Primary Adrenal Insufficiency

- **Hydrocortisone** 15-25mg daily in 2-3 divided doses
  - Highest dose in the morning (15+10 or 15+5+5mg)
- Prednisone 3-5mg once daily
- Avoid dexamethasone (risk of Cushing's & difficult to titrate)
- Monitor clinical parameters: blood pressure, weight, energy level, diabetes
- No need to monitor cortisol level
- Fludrocortisone can cause increased BP
- DHEA supplement in women with low libido, depression, low energy

Management & Prevention of acute adrenal crisis

- Education is important, Steroid emergency card, MedicAlert

- Main precipitant: GI disease & flu-like illness

- Some medications can increase cortisol metabolism, e.g. thyroxine, carbamazepine, St John's wort

- Double (>38C) or triple (>39C) the usual daily dose until recovery, or 2-3 days

- Sick day rule 1: fever, illness requiring bed rest, needs antibiotic, before small OP procedure (eg dental work) – to double/triple oral dose

- Sick day rule 2: severe illness, trauma, persistent vomiting, needs fasting or procedure or surgery – for IV hydrocortisone

- Suspected adrenal crisis: IV Hydrocortisone 100mg, then 200mg/24h

- Fluid resuscitation, treat hypoglycaemia

- Rapid tapering or switch back to oral

Polyglandular autoimmune syndromes (PAS)

PAS1

Mutation in the AIRE gene (autoimmune regulator gene)

Chronic mouth & nail moniliasis in childhood, then primary AI and primary hypoparathyroidism

Increased prevalence of urticarial eruption, hepatitis, gastritis, intestinal dysfunction, pneumonitis, and Sjögren-like syndrome

PAS2

Presents in childhood & early adulthood

Type 1 diabetes, Hashimoto's throiditis, coeliac, pernicious anaemia, thrombocytopenic purpura

Secondary Adrenal Insufficiency - Causes

1. Panhypopituitarism
2. Isolated ACTH deficiency
3. Traumatic brain injury
4. Genetic
5. Familial CBG deficiency (rare)
6. Drugs (high dose progestin (megestrol); long term opiate, especially if dose>100mg of morphine equivalent daily dose)

Tertiary Adrenal Insufficiency - Causes

1. Chronic high dose glucocorticoid therapy

- supresses HPA axis

- decrease CRH production

- blocks ACTH secretion -> atrophy of zona fasciculata and zona reticularis

2. After the cure of Cushing's syndrome

- pre-surgery high cortisol had suppressed the the HPA axis

3. Other hypothalamus causes (sarcoidosis, tumour, cranial irradiation)

4. Isolated CRH deficiency (rare)

5. Some Prader-Willi syndrome (partial adrenal insufficiency)

Secondary AI – clinical features

- Few symptoms similar to primary AI (weakness, fatigue, muscle/joint pain, psychiatric manifestation)

- ***Absent*** : hyperpigmentation (no ↑ ACTH)

- Dehydration not present, hypotension less prominent

- Hyperkalemia not present (aldosterone is present)

- GI symptoms less common

- **Hypoglycaemia *more common***

- May have pituitary tumour symptoms (headache, visual field defect)

Glucocorticoid withdrawal

- Prolonged administration of glucocorticoids (GC) is by far the most common cause of ACTH deficiency and adrenal insufficiency.
- GC is often used in RA, SLE, small vessel vasculitis, PMR, inflammatory bowel disease
- Steroid-induced side effects generally require tapering of the drug as soon as the disease being treated is under control

- Patients treated with GC rarely present with adrenal crisis, although sudden withdrawal of glucocorticoids can result in exacerbation of the disorder for which they were being given (eg, asthma, inflammatory disease, or organ transplantation), symptoms of glucocorticoid deficiency, or hypotension.
- Tapering must be done carefully to avoid both recurrent activity of the underlying disease, and possible cortisol deficiency resulting from HPA suppression during the period of steroid therapy.

Glucocorticoid withdrawal - Indications

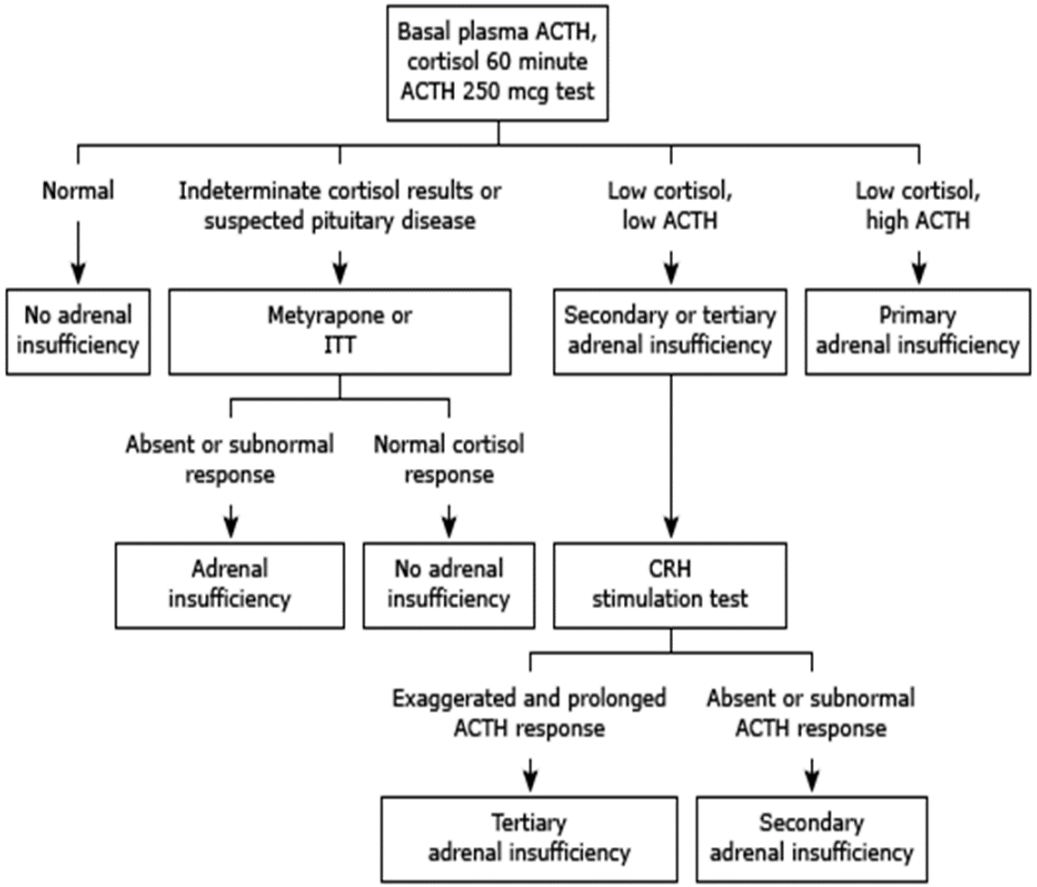
Tapering or gradual withdrawal:

1. When the maximum desired therapeutic benefit has been obtained
2. When inadequate therapeutic benefit has been obtained after an adequate trial
3. When side effects, such as osteoporosis or hypertension, become serious or uncontrollable with medication

Immediate cessation or rapid reduction of steroid when:

1. Steroid-induced acute psychosis that is unresponsive to antipsychotic medications
2. Herpesvirus-induced corneal ulceration, which can rapidly lead to perforation of the cornea and possibly permanent blindness

Diagnostic approach of suspected adrenal insufficiency



1. Check 8am cortisol & ACTH
2. If 8am cortisol <200, to arrange for **Short Synacthen Test** (can be done at Greenlane Clinical Centre)
3. Check other pituitary hormones if ACTH is low <2
4. Check Na & K
5. If suspect primary AI, check aldosterone, renin & DHEAS + adrenal antibody

Short Synacthen Test

- ACTH stimulation test
- Indicated if cortisol <200, more so if <170 nmol/L (LabPlus)
- Check baseline cortisol
- IV Synacthen 250mcg given
- Recheck cortisol after 30 minutes
- If cortisol >400: normal
- If cortisol <400, likely has adrenal insufficiency (primary or secondary), or adrenal suppression from exogenous steroid (if on estrogen or OCP, AI suspected if cortisol <600)

Back to case one

16 y/o girl

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Mum noted "moon face"

8am cortisol tested and it is low <14 nmol/L (normal 150-540)

Questions:

1. diagnosis : adrenal insufficiency from exogenous steroid use, ?moon face due to Cushing's

2. management : assess efficacy of triamcinolone, ?could taper off or stop steroid, ?any symptoms of ?hydrocortisone 20mg od then wean down by 5mg every month

Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)	Anti-inflammatory activity relative to hydrocortisone (HC)	Duration of action (hours)
Hydrocortisone	20	1	8-12
Prednisone	5	4	12-36
Methylprednisolone	4	5	12-36
Triamcinolone (Kenacort-A, Kenalog; Aristocort cream)	4	5	12-36
Dexamethasone	0.75	30	36-72
Betamethasone (Beta cream, Diprosone, Betnovate; Fucicort)	0.6	30	36-72

Take home messages

- Symptoms of adrenal insufficiency could be of gradual onset and non specific

- Commonest reason for AI is prolonged exogenous glucocorticoid treatment

- Addison's disease main cause of primary AI (look for hyperpigmentation)

- Pituitary problems cause secondary AI (pigmentation, hypotension rare, hypoglycaemia more common)

- Suspect AI if 8am cortisol <170 – can then arrange for Synacthen test

- Primary AI if ACTH 2x more than normal (normal 2-11 pmol/L) with low cortisol

- Hydrocortisone 15-25mg/day is the usual maintenance dose.

- Also use fludrocortisone in primary AI, +/- DHEA for women with low libido, loss of axilla/pubic hair and low energy

- It is important to prevent adrenal crisis

- "Sick day rules": double or triple the Hydrocortisoone dose during acute illness (if tolerating orally)

-Adrenal crisis: use IV Hydrocortisone, fluid resuscitation

- Always give Hydrocortisone first before thyroxine if suspect panhypopituitarism