The Adrenal Gland

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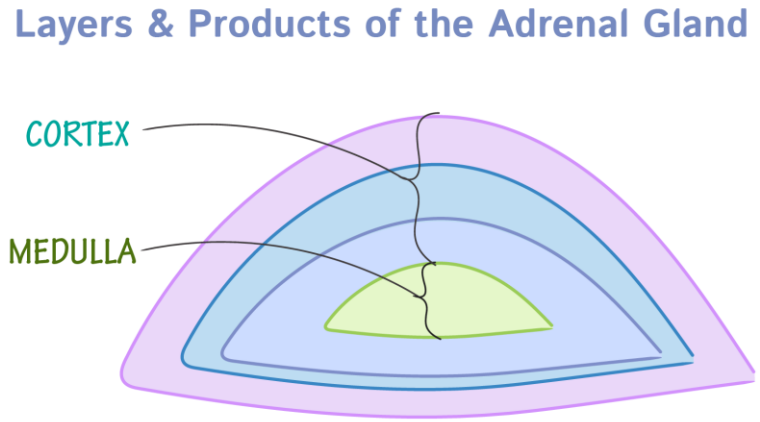
Anatomy & Physiology of Adrenal Glands

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



CORTEX	
Zona glomerulosa — Mineralocorticoids	aldosterone
Zona fasciculata — Glucocorticoids	cortisol
Zona reticularis — Androgens	DHEA, DHEAS, Androstenedione
MEDULLA	
Catecholamines	

Adrenal Pathologies

- **Excessive secretion**

– Cushing's Syndrome, Primary Aldosteronism, Phaeochromocytoma

- **Insufficiency**

– Addison's disease (primary adrenal insufficiency)

- **Tumour/Incidentaloma**

– Adrenal adenoma/carcinoma

- **Genetic disorder** (e.g. 21 hydroxylase deficiency)

– Congenital Adrenal Hyperplasia

Case one

- 58M
- HTN since 2012; PAF; GB polyps; ex-smoker
- Rx: Felodipine 5mg od, Flecainide, Dabigatran
- Parents had HTN in their 60s
- Developed new hypokalaemia 3.1-3.4, not on diuretics
- Given K since Jan19

- Aldosterone 1140 (40-1000), renin 2 (4-46), ARR 570 (<50)
- Seen in FSA Endocrine clinic - Feb19
- Repeat Aldosterone 945, renin 2, ARR 473, K 3.8 (whilst on KCl)
- TFT, HbA1c, sCr – all normal

Case one

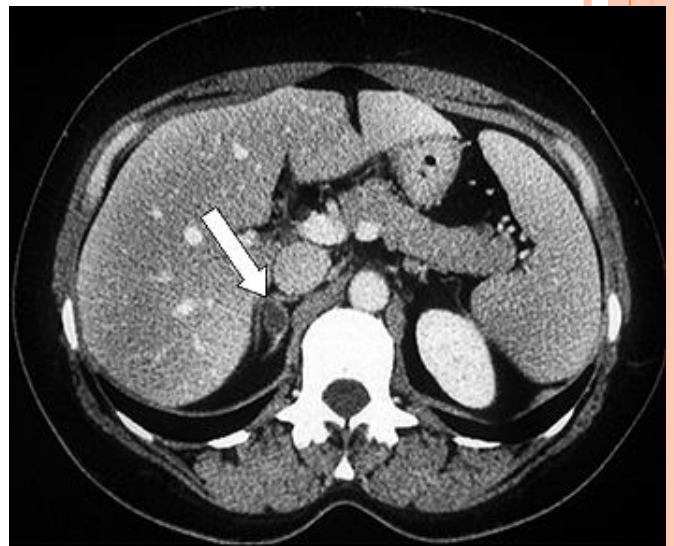
- CT Adrenal (7/3/19) – right adrenal nodule 8mm, 34HU, lipid poor; normal left adrenal
- Saline Suppression Test (SST) 22/3/19 : pre-Aldo 1120, post-Aldo 527 (should be <200) :positive SST
- Diagnosis **- Primary aldosteronism**
- 8/4/19 - Didn't want surgery or Spironolactone. Started on Eplerenone 25mg (non Pharmac funded), to stop Felodipine & K
- 29/4/19 – SBP 180-200, didn't take Eplerenone, restarted on Felo5. BP in clinic 147/90 – advised to restart Eplerenone
- 13/5/19 – BP 125/75. Now wants surgery!

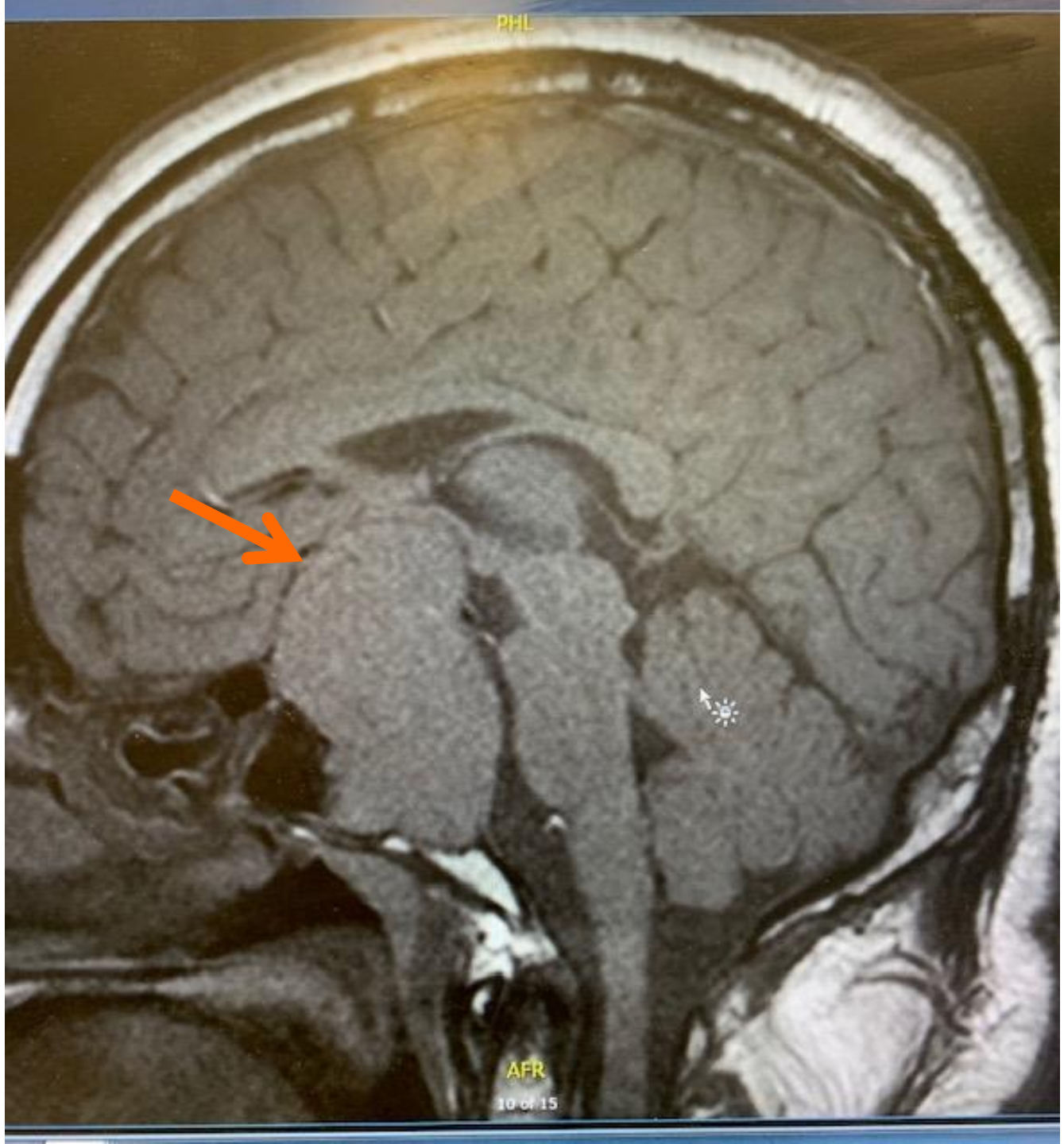
Case one

- Adrenal Vein Sampling (AVS), done on 3/7/19 (ADBH Interventional Radiology) : confirmed right lateralisation.
- Surgery on 1/10/19 (right laparoscopic adrenalectomy)
- Histology: small adenoma, no atypia
- Postop: advised to stop all anti-HTN
- 29/10/19 – BP 134/81, K 4.9; repeat Aldo-103, renin-11, ARR 9

- Primary Aldosteronism due to hypersecreting right adrenal adenoma
- ***(HTN onset age 51, positive family history, hypokalaemia, markedly raised Aldo/ARR & suppressed renin)***

- Surgically CURE!!

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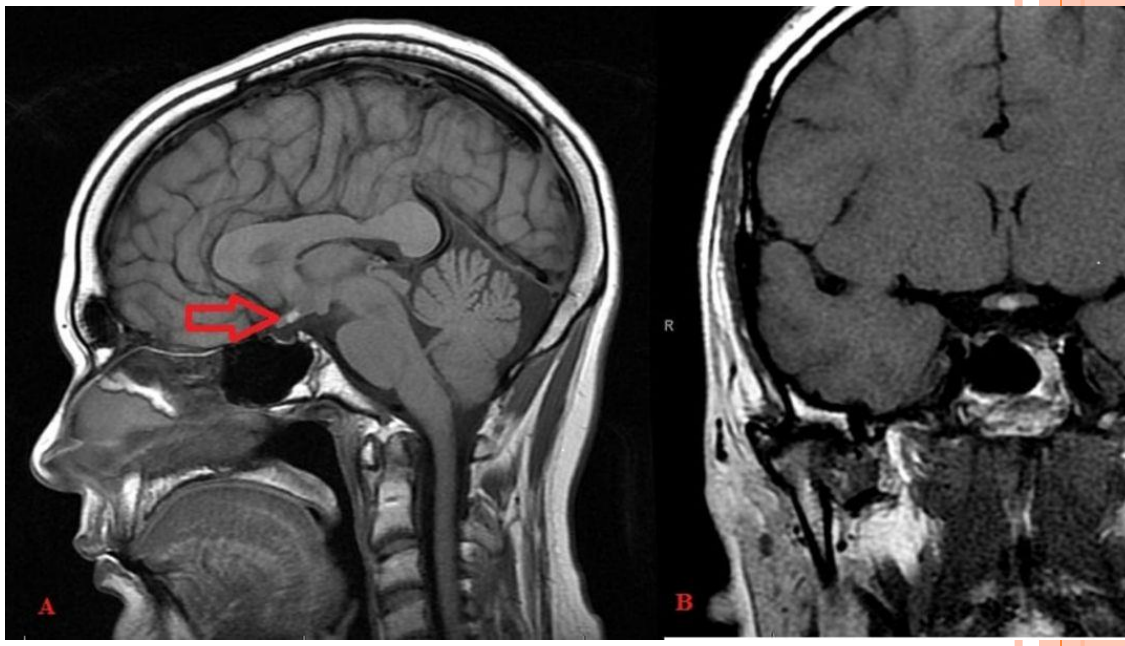
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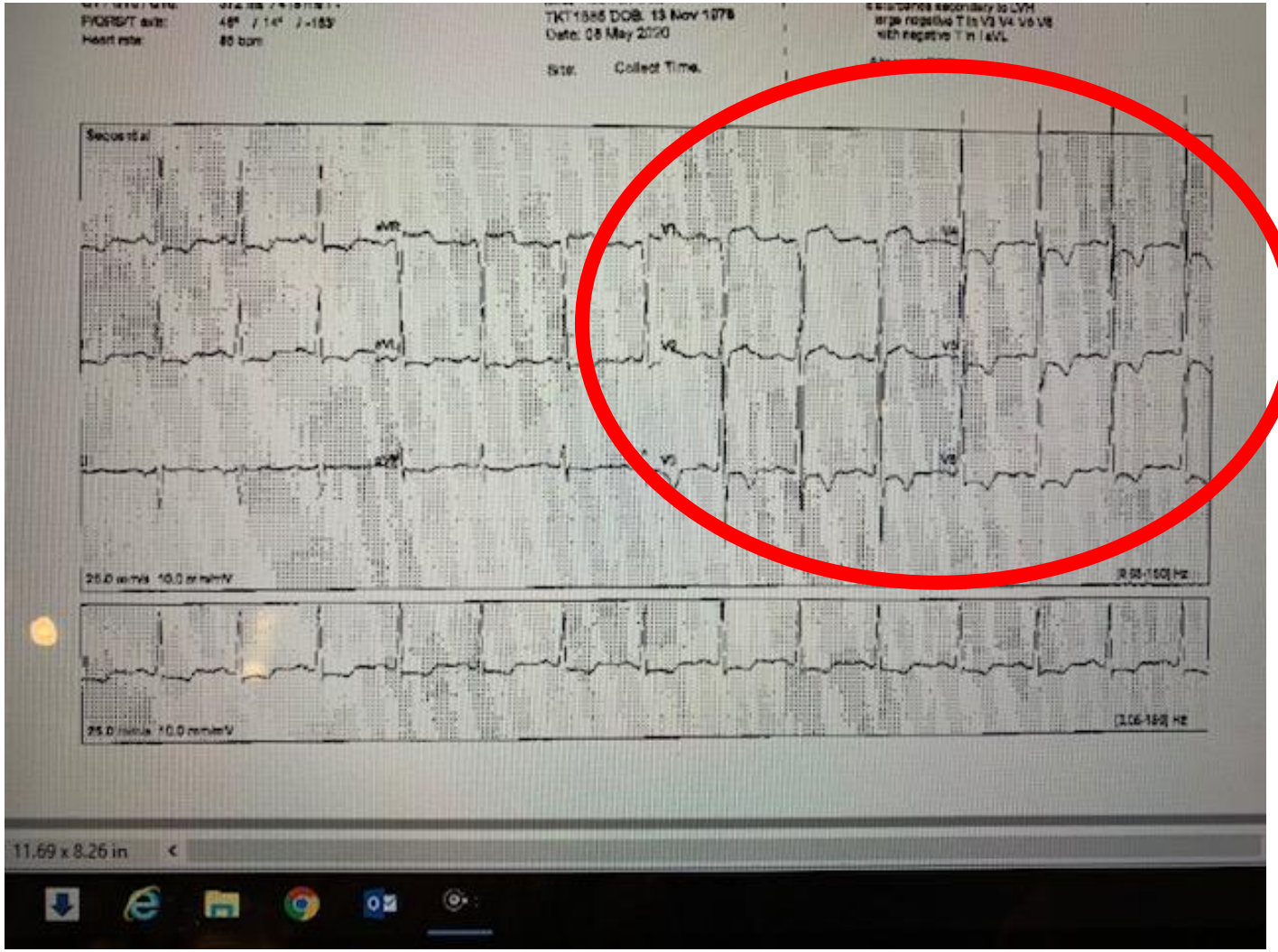
Case two

- 42F
- No PMH
- 20/3/20 – found BP 217/138 during flu vaccine. Put on Cilazapril 5mg
- COVID….4/5/20: BP 190/40, added Chlorthalidone 12.5mg od and Amlodipine 5mg od
- Father had HTN in old age
- Non smoker
- Weight 74kg, height 170cm (used to be 90kg)
- Labs: normal plasma metanephrines
- Aldosterone **1000** (40-1000), renin 17, ARR **59**; K 3.7 (normal)

Case two - ECG



Case two

- CT Adrenal (20/5/20) – **no** adrenal adenoma. Both adrenals are normal in size, shape & density
- SST (26/6/20) – pre-Aldo 572, post-Aldo **335** (<200)
- 2/7/20 – BP 138/98 (on Chlorthalidone 25, Amlodipine 7.5, Cilaz 5)
- AVS (WDHB, 9/7/20) – NO lateralisation

- **Primary Aldosteronism, no adenoma or lateralisation**

  (***uncontrolled young HTN, normal K, borderline ↑ Aldo, non-suppressed renin, raised ARR, positive SST***)

- 30/7/20 – BP 134/92
- For medical treatment, started on Spironolactone 25mg od
- Due for U&Es in 4 weeks time & clinic FU to review BP (also self monitor)

Primary Aldosteronism

- Non suppressible (primary) hypersecretion of aldosterone
- Often underdiagnosed
- Classic clinical features: hypertension, hypokalaemia (but in 9-40% cases only)
- Most common subtypes: (a) unilateral adenoma ; (b) bilateral adrenal hyperplasia
- Other subtypes: unilateral adrenal hyperplasia, carcinoma, familial hyperaldosteronism

- Prevalence: 3-12% (primary care) 1-30% (tertiary/referral centre)
- A frequent cause of secondary hypertension

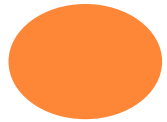
Primary Aldosteronism

Identify PA is important!

- Higher rate of CV mortality compared to primary HTN
- Treatment could reverse the CV risk

Who should be tested/screened?

1. Hypertension and spontaneous hypokalaemia
2. Severe HTN (>150/>100)
3. Drug resistant HTN (on >3 agents)
4. HTN with adrenal incidentaloma
5. Young onset HTN or CVA <40yrs or FH of young HTN
6. Family history of PA



Primary Aldosteronism – CONFIRM DIAGNOSIS

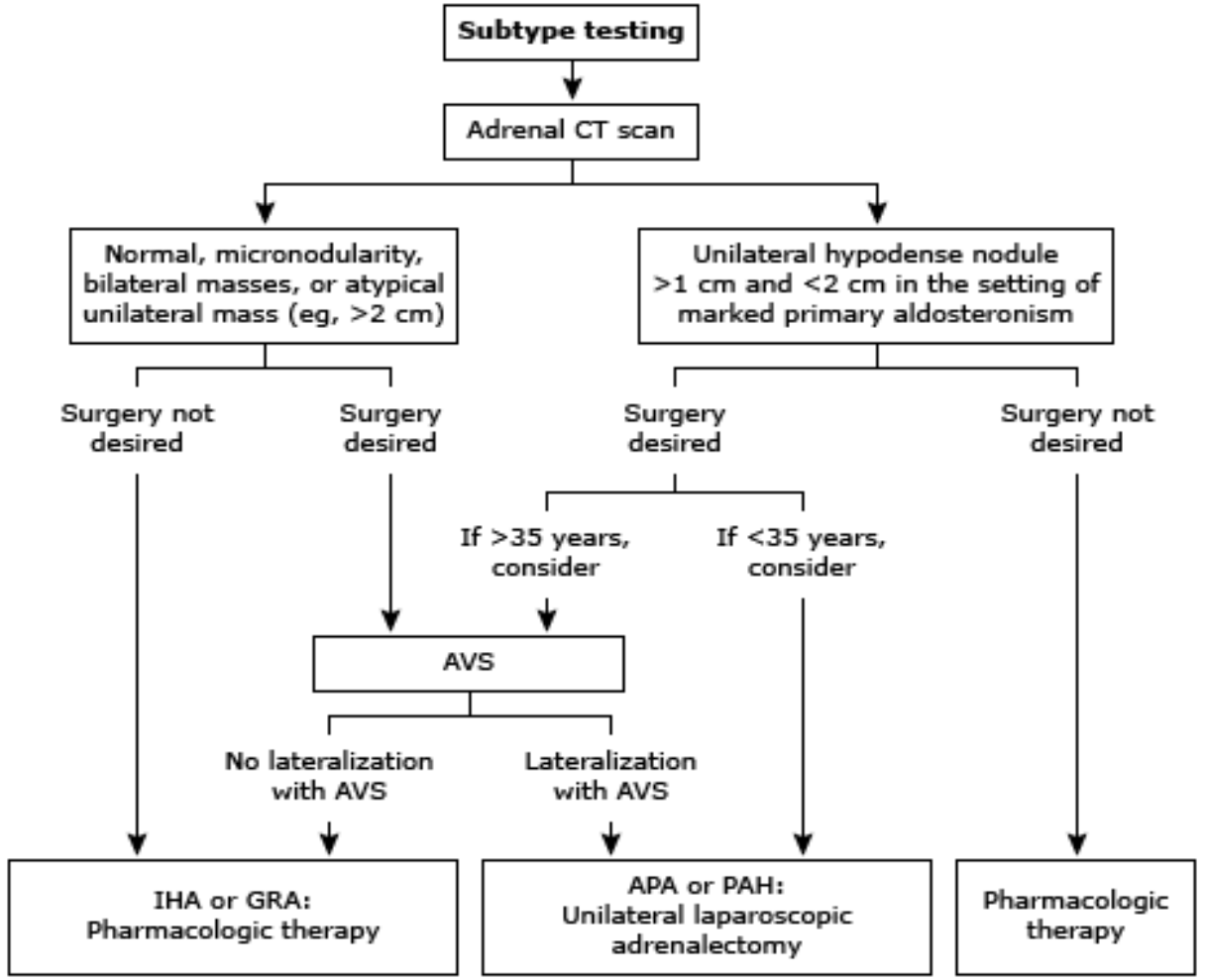
- Saline Suppression Test (SST)
- To suppress endogenous aldosterone production
- Infuse 2L of 0.9% saline over 4 hours (8am-12noon)
- Post SST aldosterone should be <200 pmol/L
- Must correct hypokalaemia before hand (low K suppresses aldosterone production)

Primary Aldosteronism - subtype classification

- Unilateral (aldosterone producing adenoma) *vs B*ilateral adrenal hyperplasia (BAH)

- Somatic mutations in *KCNJ5*, *ATP1A1*, *ATP2B3*, *CTNNB1*, and *CACNA1D* are found in more than 50 percent of resected unilateral adrenal adenomas

- BAH, which accounts for approximately 60 percent of cases, is generally a milder disease with less hypersecretion of aldosterone and less hypokalemia.
Its cause is not yet determined.

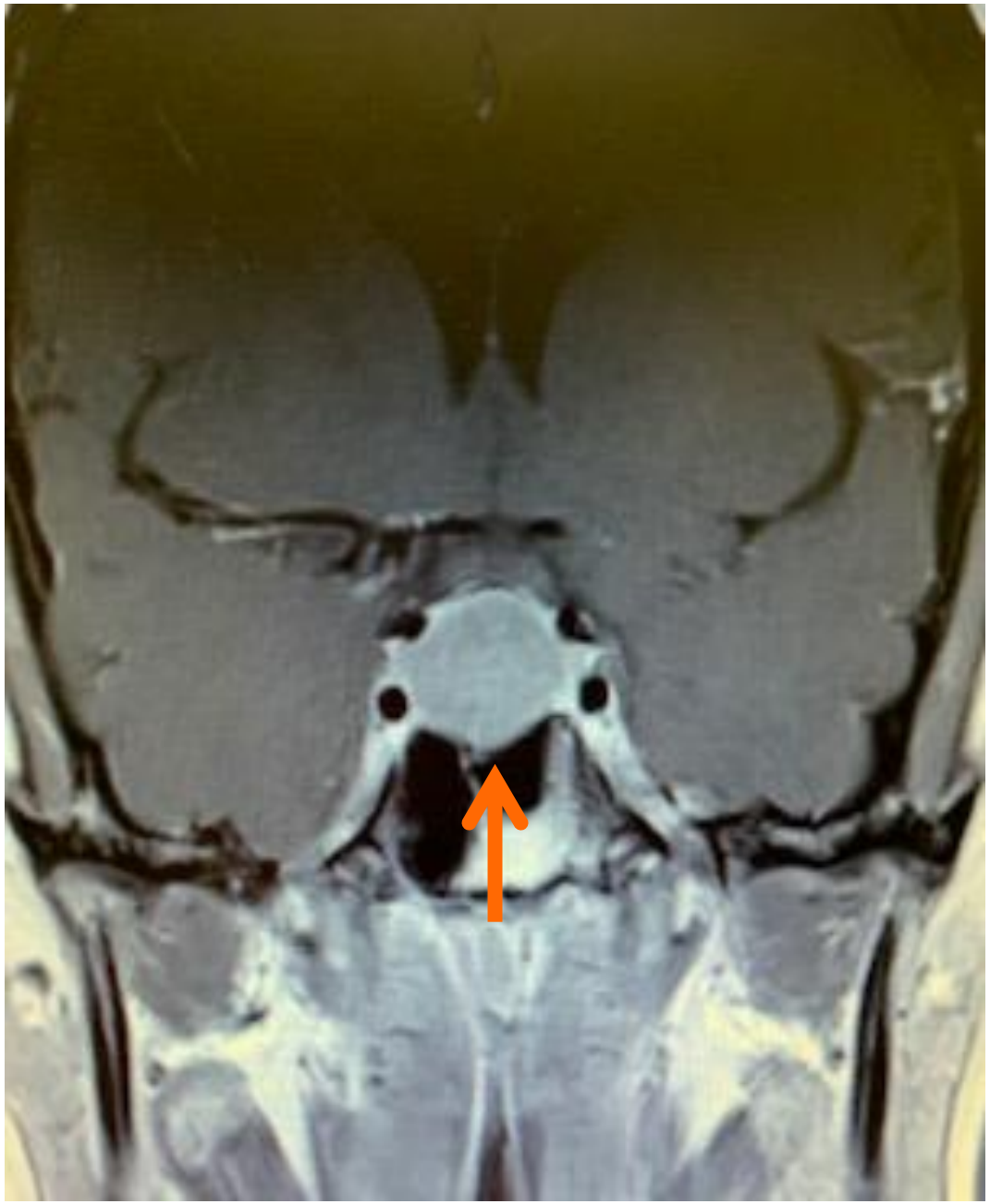


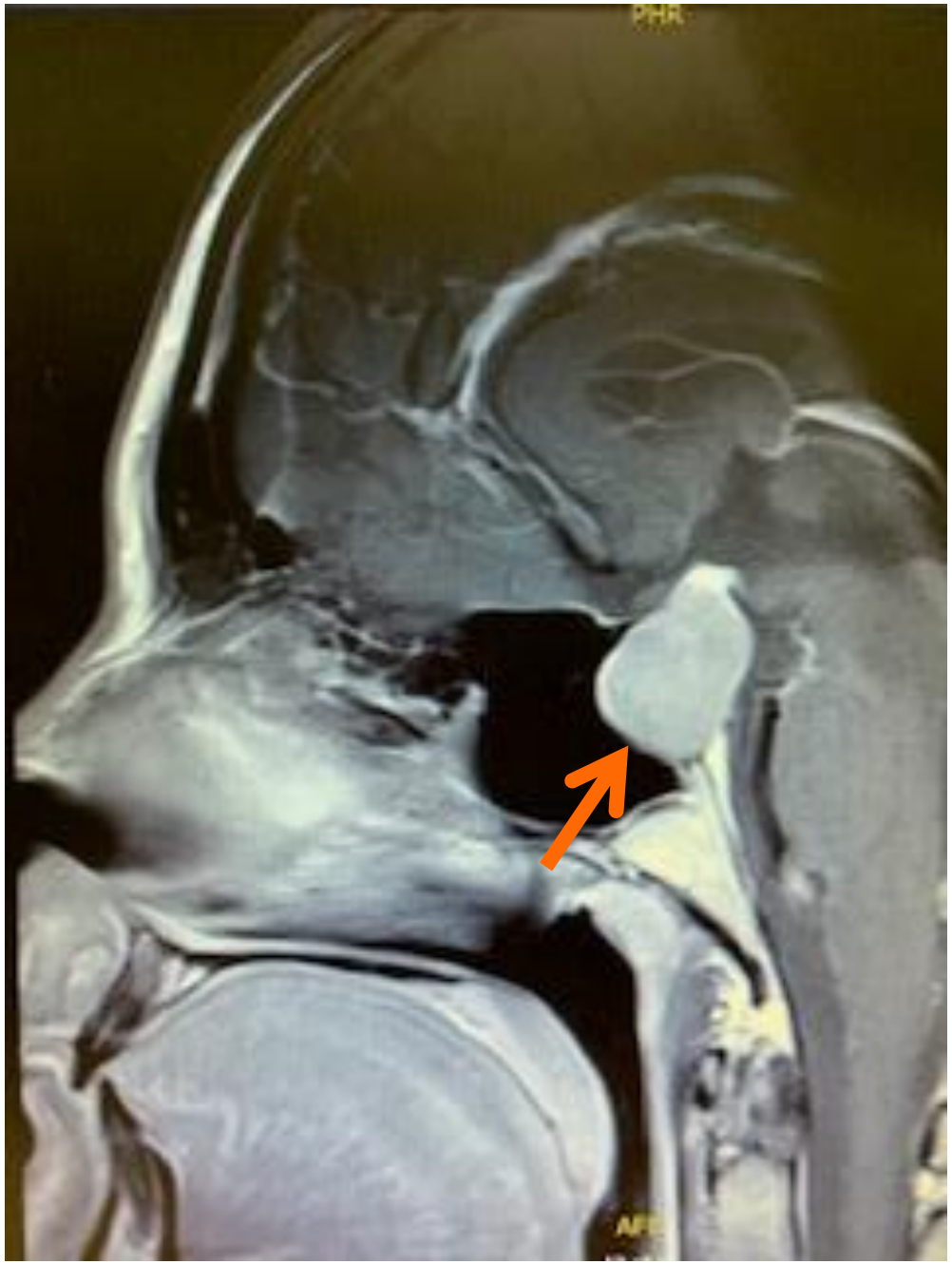
Primary Aldosteronism - treatment

Objectives: to normalise BP and K; and to reverse CV adverse effects of hyperaldosteronism

- Unilateral aldosterone hypersecretion: surgery (laparascopic adrenalectomy)
- Post op: measure aldosterone, stop spironolactone & other anti-HTN, monitor potassium

- BAH or poor surgical candidate: medical (mineralocorticoid antagonist – Spironolactone or Eplerenone




PHR

Case three

- 39F
- No PMH
- Presented in January20 with hypertension (170/80), ~20kg weight gain, insomnia, anxiety, round face, muscle weakness, clumsiness, stretch mark on abdomen, nocturia, oligomenorrhoea, hand tremor, hirsutism, oily skin.
- Onset of symptoms probably over last 3 years

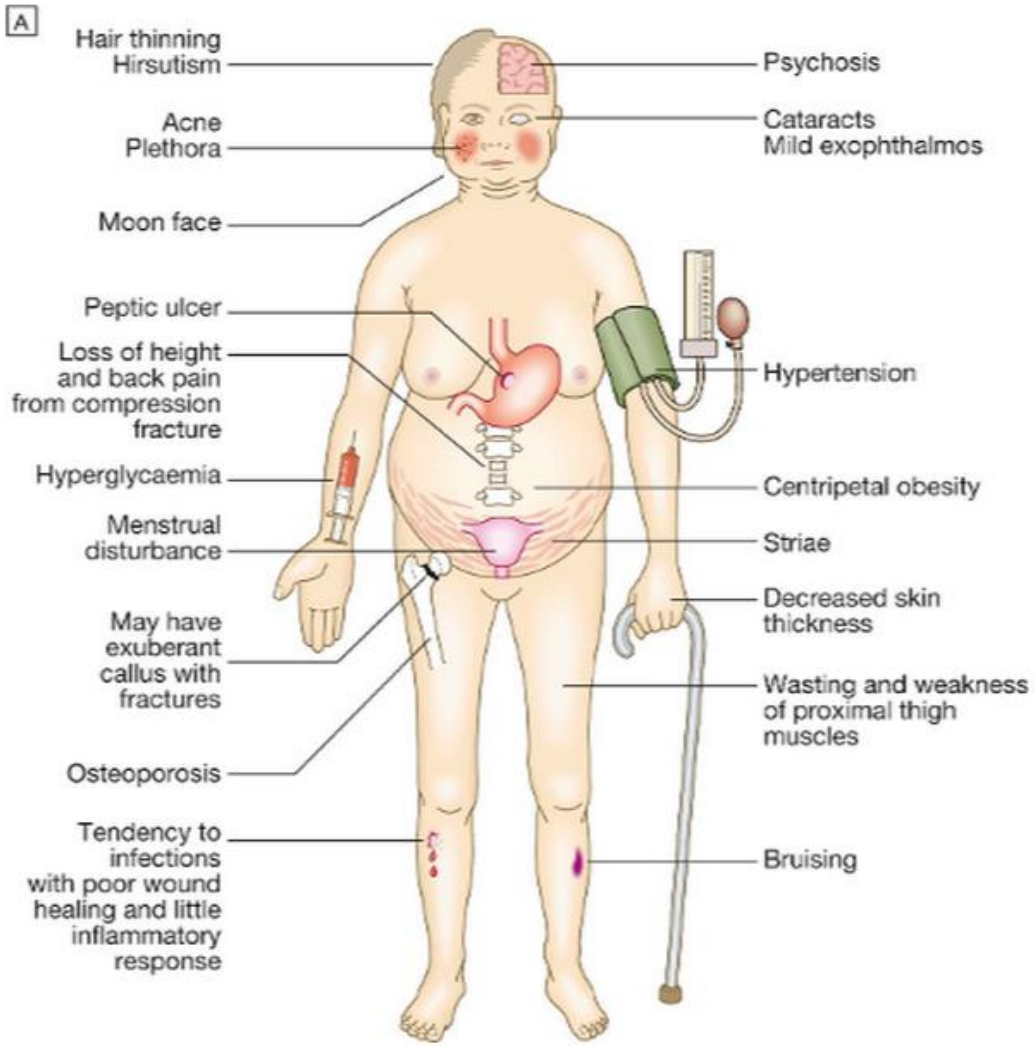
- Random cortisol 724 nmol/L; ACTH<1 (2-11)
- 24h urinary free cortisol (UFC) 3007 nmol/day (normal <350)
- 1mg overnight dexamethasone suppression test (DST) 700 nmol/L (normal <50)
- HbA1c 36, normal TFT & plasma metanephrines

Case three

- **Cushing's Syndrome (CS)**
- 2x Positive screening tests for CS (24h UFC & 1mg DST)
- Further investigations:
  - CT Adrenal : right adrenal adenoma 31x23x27mm, 28HU

- Initial treatment: Amlodipine, later changed to Losartan
- Later started on Metyrapone 250mg tds (pre-op) for symptom relief

- Right laparoscopic adrenalectomy in March 20
- Post-op hydrocortisone started



Signs and symptoms of Cushing's syndrome

More common	Less common
▪ Decreased libido ▪ Obesity/weight gain ▪ Plethora ▪ Round face ▪ Menstrual changes ▪ Hirsutism ▪ Hypertension ▪ Ecchymoses ▪ Lethargy, depression ▪ Dorsal fat pad ▪ Abnormal glucose tolerance	▪ ECG abnormalities or atherosclerosis ▪ Striae ▪ Edema ▪ Proximal muscle weakness ▪ Osteopenia or fracture ▪ Headache ▪ Backache ▪ Recurrent infections ▪ Abdominal pain ▪ Acne ▪ Female balding

ECG: electrocardiogram.

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Cushing's Syndrome – who to test?

- Unusual findings for age (young HTN / osteoporosis)
- Resistant (severe) HTN / osteoporosis at any age
- Predictive CS features – facial plethora, proximal myopathy, wide (>1cm) purple striae, easy bruising
- Adrenal incidentalomas

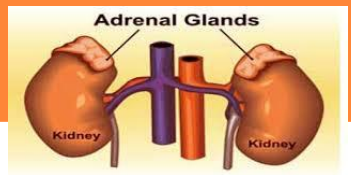
- Should **NOT** screen for CS on those who take exogenous glucocorticoid
- Drug history is very important (including herbal remedy, supplement, OTC products, inhaler, cream/ointment, eyedrop)

Cushing's Syndrome – confirm diagnosis

- 24h UFC
- 1mg overnight DST
- Midnight salivary cortisol

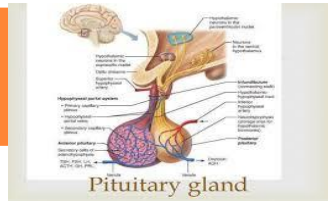
Cushing's Syndrome - causes

ACTH independent



- Adrenal adenoma (10%)
- Adrenal carcinoma >4cm (8%)
- Micronodular (1%) or macronodular (1%) hyperplasia

ACTH dependent

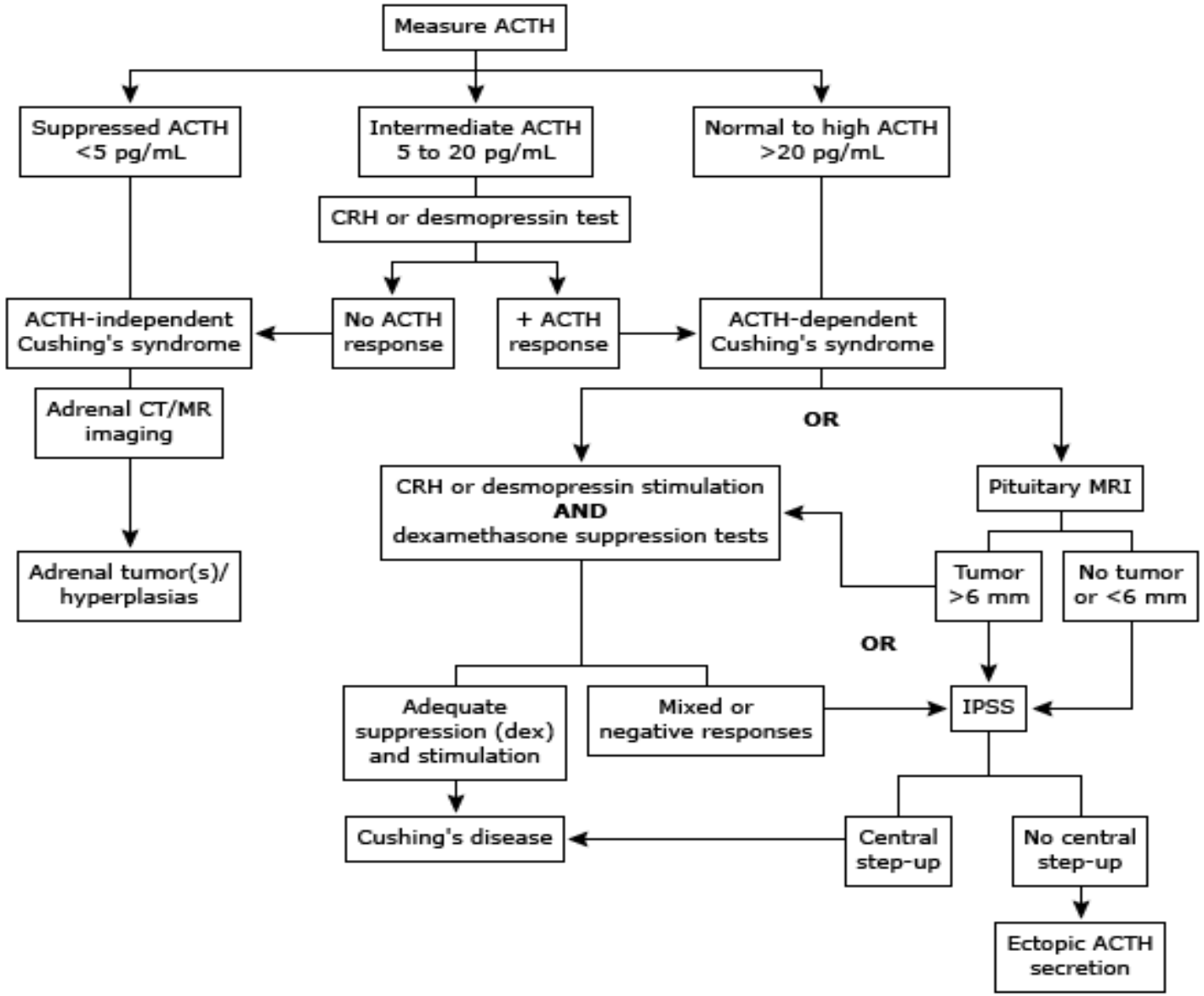


- Cushing's disease (70%)
- Ectopic ACTH (12-15%)
- Ectopic CRH (<<1%)

Pseudo-Cushing's syndrome
1. Major depression (1%)
2. Alcoholism (<1%)

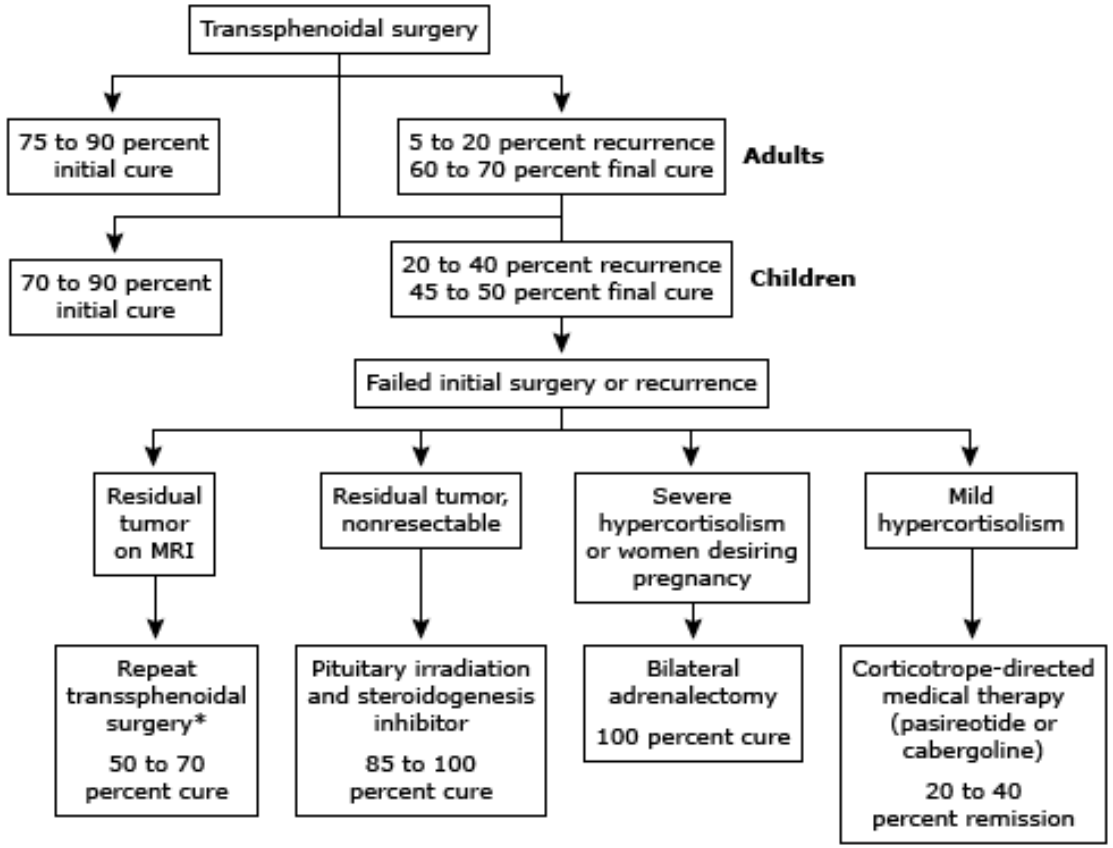
Exogenous corticosteroid

Establishing cause of CS – adrenal vs pituitary



Cushing's syndrome - treatment

- Complete removal of either ACTH-secreting pituitary, cortisol-secreting adrenal or ectopic ACTH-secreting tumour



Adrenal adenoma/bilateral adrenal hyperplasia

- Unilateral or bilateral adrenalectomy
- Postoperative glucocorticoid therapy is needed because excess cortisol secretion has suppressed CRH and ACTH – months to years
- Pre-op VTE prophylaxis (10x risk!)

- adrenal enzyme inhibitors (metyrapone or ketoconazole) can be given to reduce cortisol secretion in an attempt to improve the patient's physical condition *before* surgery.

Adrenal Insufficiency

- 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**, autoimmune isolated ACTH deficiency (rare)
3. Tertiary – **chronic high dose steroid**, cure of CS

Adrenal Insufficiency - clinical features

Acute (adrenal crisis)

- Shock
- Anorexia
- Vomiting
- Abdominal pain
- Lethargy/lassitude
- Fever
- Confusion
- Coma

Chronic

Onset can be insidious, gradual, non specific

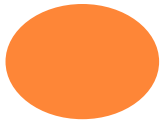
- Fatigue
- Weight loss
- Anorexia, Dehydration
- N + V, abdo pain
- Muscle & joint pain
- Hyperpigmentation
- Vitiligo (autoimmune)
- Can be a/w T1D, Coeliac, pernicious anaemia, TTP (polyglandular autoimmune syndrome type 2)

Adrenal Insufficiency - clinical setting/precipitating factors

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

Chronic Primary Adrenal Insufficiency - lab findings

- ↑ Na
- ↓ K
- Hyperchloreamic acidosis
- Hypoglycaemia
- Normochromic anaemia (+/- pernicious anaemia)
- *History of glucocorticoid withdrawal, nausea, hyperkalemia, and eosinophilia was a useful predictor of adrenal insufficiency in an inpatient population*



Secondary & Tertiary Adrenal Insufficiency

- Few symptoms similar to primary AI
- Absent : hyperpigmentation (no ↑ ACTH), GI symptoms, hyperkalaemia, dehydration, hypotension
- Hypoglycaemia ***more common***

Suspected Adrenal Insufficiency -diagnostic approach

1. Start with checking 8am cortisol & ACTH

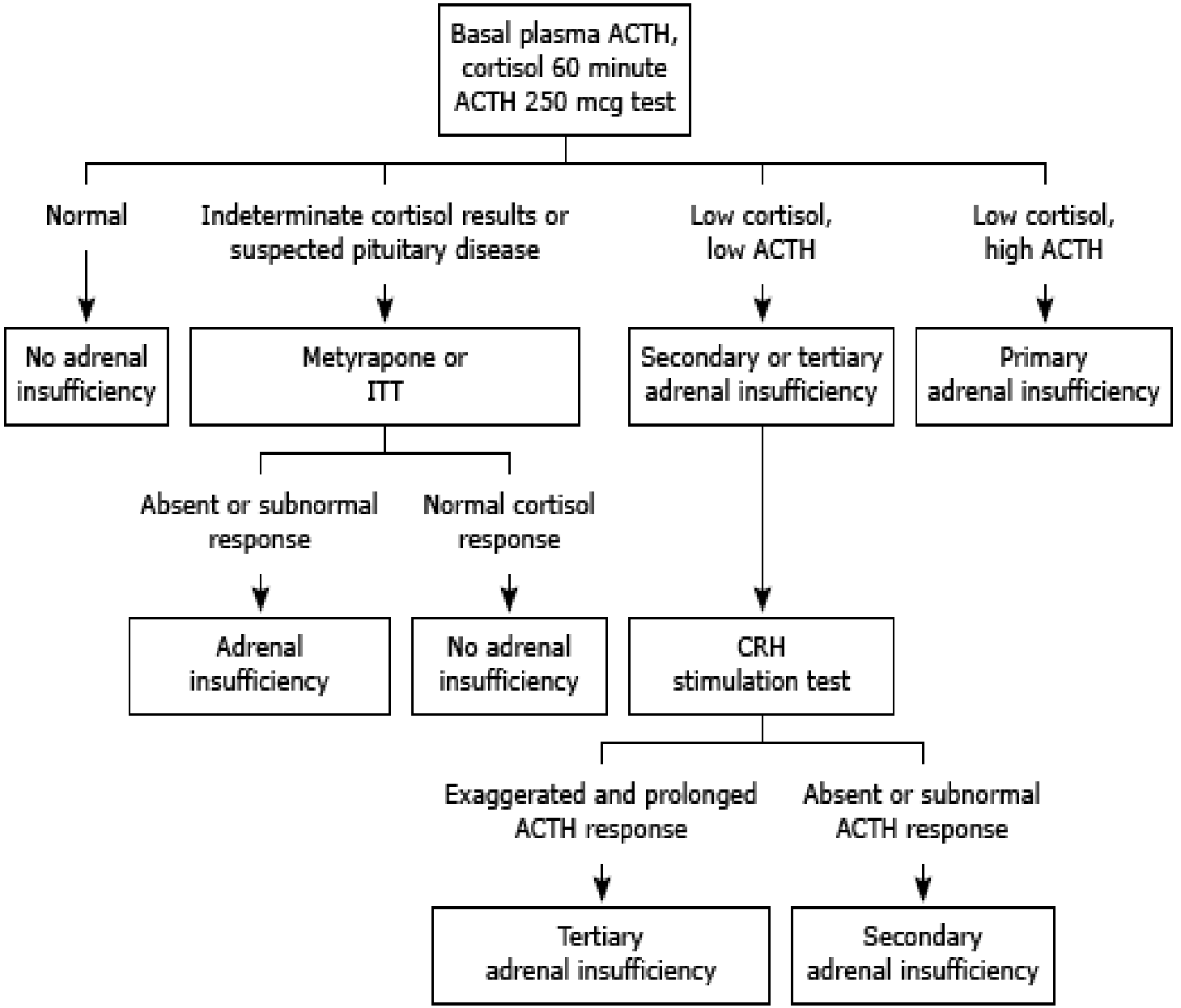
2. Aim 8am cortisol >200 nmol/L

- If <200, do Synacthen Test (can arrange with Labtests)

3. Consider checking pituitary hormones

4. Check Na & K as well

5. If suspect primary AI, check aldosterone, renin, DHEAS



Treatment of Adrenal Insufficiency

Primary

1. Acute adrenal crisis

– give IV Hydrocortisone 100mg stat, call ambulance & send to hospital

2. Chronic AI

- **glucocorticoid** : Hydrocortisone 15-25mg daily in 2-3 divided doses; or Prednisone or Dexamethasone once daily (Cushing's monitor, BP, HbA1c, bone density)
- **mineralocorticoid**: Fludrocortisone 50-100 mcg/day (adjust to aim Renin in the upper normal range, monitor BP, K, oedema)
- **?DHEAS** in women, not men (impaired mood & sense of well being)

Secondary

- pituitary hormones replacement (Hydrocortisone, Thyroxine)

Tertiary (suppression of HPA axis by chronic high dose glucocorticoid, cure of Cushing's syndrome)

- avoid abrupt cessation of glucocorticoid!

Systemic Corticosteroid comparison table

Comparison of systemic corticosteroid preparations

	Equivalent doses (mg)	Antiinflammatory activity relative to hydrocortisone*	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72
Mineralocorticoids			
Fludrocortisone	Not used for an antiinflammatory effect¶. The typical dose of fludrocortisone for mineralocorticoid replacement is 0.1 to 0.2 mg.		12 to 36

The mineralocorticoid effect of commonly administered glucocorticoids may be estimated as follows:

- When given at replacement doses, triamcinolone, dexamethasone, and betamethasone have no clinically important mineralocorticoid activity.
- 20 mg hydrocortisone and 25 mg of cortisone acetate each provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone.
- Prednisone or prednisolone given at antiinflammatory doses ≥50 mg per day provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone.

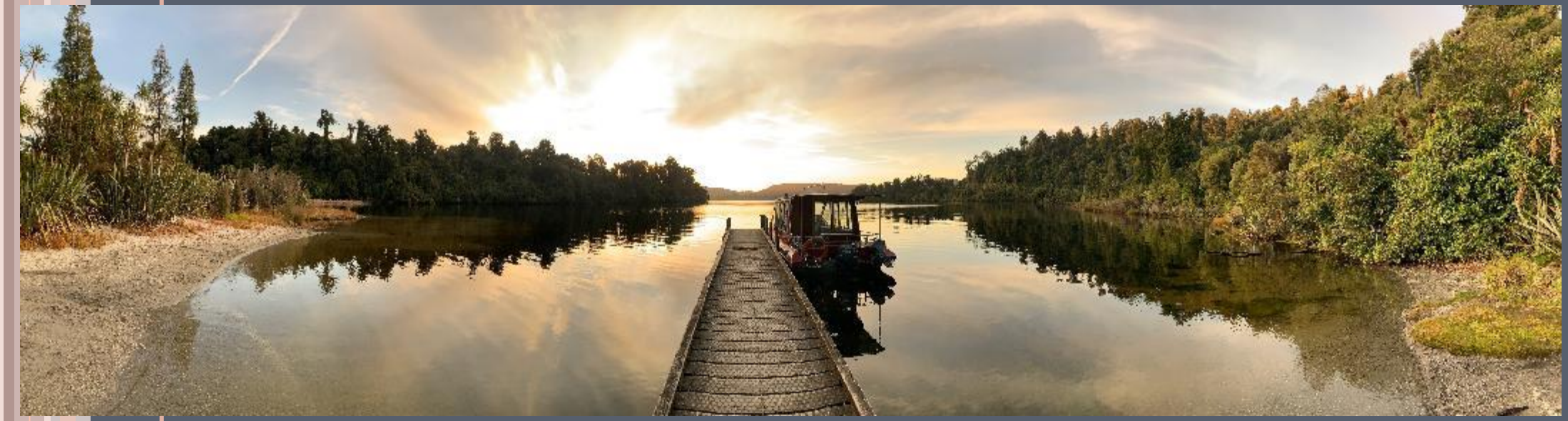
* Equivalent antiinflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intraarticular or intramuscular administration may vary considerably.
¶ The antiinflammatory potency is 10 to 15 times that of hydrocortisone; however, fludrocortisone is

Take home messages

- Primary aldosteronism is often under-diagnosed but is an important cause of (young) secondary hypertension
- Suspect PA if (1) resistant hypertension; (2) spontaneous hypokalaemia
- Cushing's syndrome is rare, many symptoms may be non specific
- Symptoms more predictive of CS include proximal myopathy, easy bruising, wide purple striae, facial plethora
- If uncertain, do screening test – 24h UFC, 1mg overnight DST, midnight salivary cortisol (random cortisol might not help)
- Other cause of secondary hypertension – phaeochromcytoma (plasma metanephrine has 99% negative predictive value)
- Adrenal insufficiency symptoms are also non specific – if in doubt, check 8am cortisol and ACTH. If cortisol <200 nmol/L needs Synacthen test.
- Avoid abrupt cessation of chronic high dose corticosteroid (risk of adrenal crisis from tertiary adrenal insufficiency)

- Myth buster – "adrenal fatigue" is not an acceptable medical/endocrinological diagnosis….

- Endocrine is simple – you either do stimulation test or suppression test….
- I am always happy to help ☺



Thank you

Questions?