REVISE NEPHROLOGY

Hypertension- who needs further investigation?

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Learning goals

- Familiarise with the indications of screening for secondary HTN
- Primary aldosteronism (PA) is the commonest cause of secondary HTN and patients often present with low/low normal K and mild alkalosis
- Understand the difference between renal artery stenosis (RAS) and fibromuscular dysplasia (FMD) both of which are grouped as renovascular HTN
- Screening and diagnostic work up of Cushing syndrome
- How and when to screen for Pheochromocytoma
- Vasculitis effecting the medium and large sized arteries can lead to HTN

HTN- mostly primary

- According to the Australian Bureau of Statistics in 2011-12 one-third (31.6%) of all adult Australians had hypertension
- Most have primary hypertension and need a basic workup: history, physical examination, ECG, electrolytes and eGFR, glucose, lipid profile and urinalysis
- Which patient needs evaluation for secondary cause of hypertension?

Need more work up.....

- Severe or resistant HTN: persistent HTN despite adequate doses of 3 antihypertensive from different classes including a diuretic
- Malignant HTN: severe HTN with signs of end-organ damage: retinal haemorrhages /papilledema, heart failure, neurologic disturbance, or AKI
- An acute rise in blood pressure developing in a patient with previously stable values or onset of hypertension after the age of 55
- Hypokalaemia and/or metabolic alkalosis in a hypertensive patient
- Adrenal incidentaloma in a hypertensive patient (screen for endocrine causes of hypertension i.e. Primary hyperaldosteronism, Cushing syndrome and Pheochromocytoma)
- Age less than 30 years in non-obese with negative family history

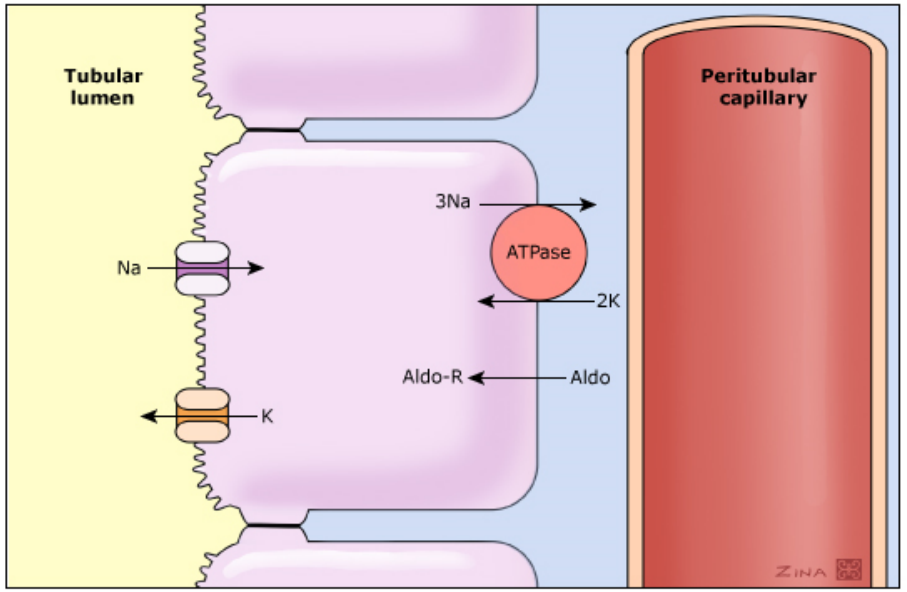
Major causes of secondary HTN

- **Primary aldosteronism – Suspect in co-existent low or low-normal K, and/or metabolic alkalosis (causes hypertension in up to 10% essential hypertension)**
- **Renovascular hypertension – Characterised by stenosis of the renal artery, relatively common in those with severe and acute hypertension**
- Cushing's syndrome
- Pheochromocytoma – Relatively uncommon cause of hypertension with about half the patients presenting with paroxysmal hypertension
- Drugs- OCP, NSAID, glucocorticoids, decongestants e.g. pseudoephedrine, cyclosporine, tacrolimus, EPO, amphetamines and cocaine
- Primary renal disease – Both acute and chronic kidney disease, particularly with glomerular or vascular disorders, can lead to hypertension

Rarer causes of HTN

- Endocrine disorders- Hypothyroidism and hyperparathyroidism
- Coarctation of aorta
- Polyarteritis Nodosa or Takayasu Arteritis
- Conditions other than primary aldosteronism leading to hypertension with metabolic alkalosis and hypokalaemia:
  - Liddle Syndrome
  - Chronic liquorice ingestion
  - Apparent mineralocorticoid excess (AME)
  - Familial Hyperaldosteronism e.g. Glucocorticoid remediable hypertension

Ion transport in collecting tubule principal cells



Schematic representation of sodium (Na) and potassium (K) transport in the sodium-reabsorbing principal cells in the collecting tubules. The entry of filtered sodium into these cells is mediated by selective sodium channels in the apical (luminal) membrane; the energy for this process is provided by the favorable electrochemical gradient for sodium (cell interior electronegative and low cell sodium concentration). Reabsorbed sodium is pumped out of the cell by the Na-K-ATPase pump in the basolateral (peritubular) membrane. The reabsorption of cationic sodium makes the lumen electronegative, thereby creating a favorable gradient for the secretion of potassium into the lumen via potassium channels in the apical membrane. Aldosterone (Aldo), after combining with the cytosolic mineralocorticoid receptor (Aldo-R), leads to enhanced sodium reabsorption and potassium secretion by increasing both the number of open sodium channels and the number of Na-K-ATPase pumps. The potassium-sparing diuretics (amiloride and triamterene) act by directly inhibiting the epithelial sodium channel; spironolactone acts by competing with aldosterone for binding to the mineralocorticoid receptor.

Primary Aldosteronism (Conn's syndrome)

- Hypokalaemia and metabolic alkalosis (potassium low normal in > 50% cases)
- ***Incidence in the 'essential hypertensive' population may be as high as 10%***
- Types:

  - Bilateral idiopathic hyperaldosteronism (60 to 70 percent)

  - Unilateral Aldosterone producing adenoma (30 to 40 percent)

- Less common forms include:

  -Unilateral adrenal hyperplasia ; aldosterone-producing adrenocortical carcinomas

  - **Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism [GRA]),** type II (the familial occurrence of APA or bilateral IHA or both with no genetic abnormality identified yet), type III (germline mutations in the *KCNJ5* potassium channel), type IV (germline mutations in *CACNA1H* (encoding T-type calcium channel)

Diagnosis of Primary Aldosteronism

- Plasma aldosterone concentration to plasma renin activity ratio (PAC/PRA) ratio above 30 strongly predictive
- Remember this ratio is denominator dependent- while the aldosterone level may be high normal**, renin is severely suppressed**

Q. Why is a raised aldosterone by itself not enough for diagnosis?

- Confirm with oral sodium loading or saline infusion test: After 3 days of oral salt loading or two litres of NaCl over 8 hours in normal people urinary and plasma aldosterone should fall
- Adrenal CT scan
- Adrenal vein sampling to differentiate adenoma (treatment surgical) vs hyperplasia (medical treatment) may be needed

Renovascular hypertension

- 10 to 45 % of those with acute or severe hypertension
- Potentially curable
- Two types: fibromuscular dysplasia(FMD) in 10-15% and most of remaining atherosclerotic renal artery stenosis (RAS)
- FMD: Commoner in women below 50 years age and unrelated to lipid status (lesions distal to proximal 2 cms of aortic origin of renal artery)
- RAS: Usually after 50 years and cholesterol plaque obstructs renal artery (lesions usually within 2 cms of origin from aorta)

When to suspect Renovascular HTN?

- Elevation in the serum creatinine by > 30 % within a week of starting ACEI or ARB
- Severe hypertension in a patient with an unexplained atrophic kidney or asymmetry in renal sizes of >1.5 cm
- Onset of severe and usually rapid hypertension after the age of 55
- A systolic-diastolic abdominal bruit that lateralizes to one side: low sensitivity (40 %) but very high specificity (99 %)

- ***Hypokalemia and alkalosis classically associated with primary aldosteronism may be seen in renovascular HTN (effect of secondary hyperaldosteronism due to activated RAAS***)

- *AND ONE MORE SCENARIO……..??*

One more scenario

- Recurrent presentations with flash pulmonary oedema and refractory heart failure
- Keeps getting echocardiograms…troponins…diuresis…..keeps coming back…..
- **Please think about bilateral renal artery stenosis**

Fibromuscular Dysplasia (FMD)

- Noninflammatory, nonatherosclerotic disorder that leads to arterial stenosis, occlusion, aneurysm, and dissection
- Approximately 2/3rd of patients have multiple arteries involved and extracranial cerebrovascular arteries (carotid and vertebral arteries) in 65%
- Commoner in women with mean age of diagnosis 52 years
- May present with severe HTN, stroke, MI or rarely spontaneous coronary artery dissection
- String of beads appearance of renal artery on CTA; stenosis distal to the first 2 cms of renal artery origin (unlike atherosclerotic renal artery stenosis)

Diagnosis of Renovascular HTN

- While the gold standard is renal angiography, it is invasive
- Any of the following three are good alternatives-

-*Duplex Doppler ultrasonography*: inexpensive but time consuming and operator dependent

-*Computed tomographic angiography (CTA*)

-*Magnetic resonance angiography (MRA):offers inconsistent detection of FMD and is performed if CTA is contraindicated*

REMEMBER THOUGH: Diagnostic tests **justified only if** a corrective procedure would be performed as treatment

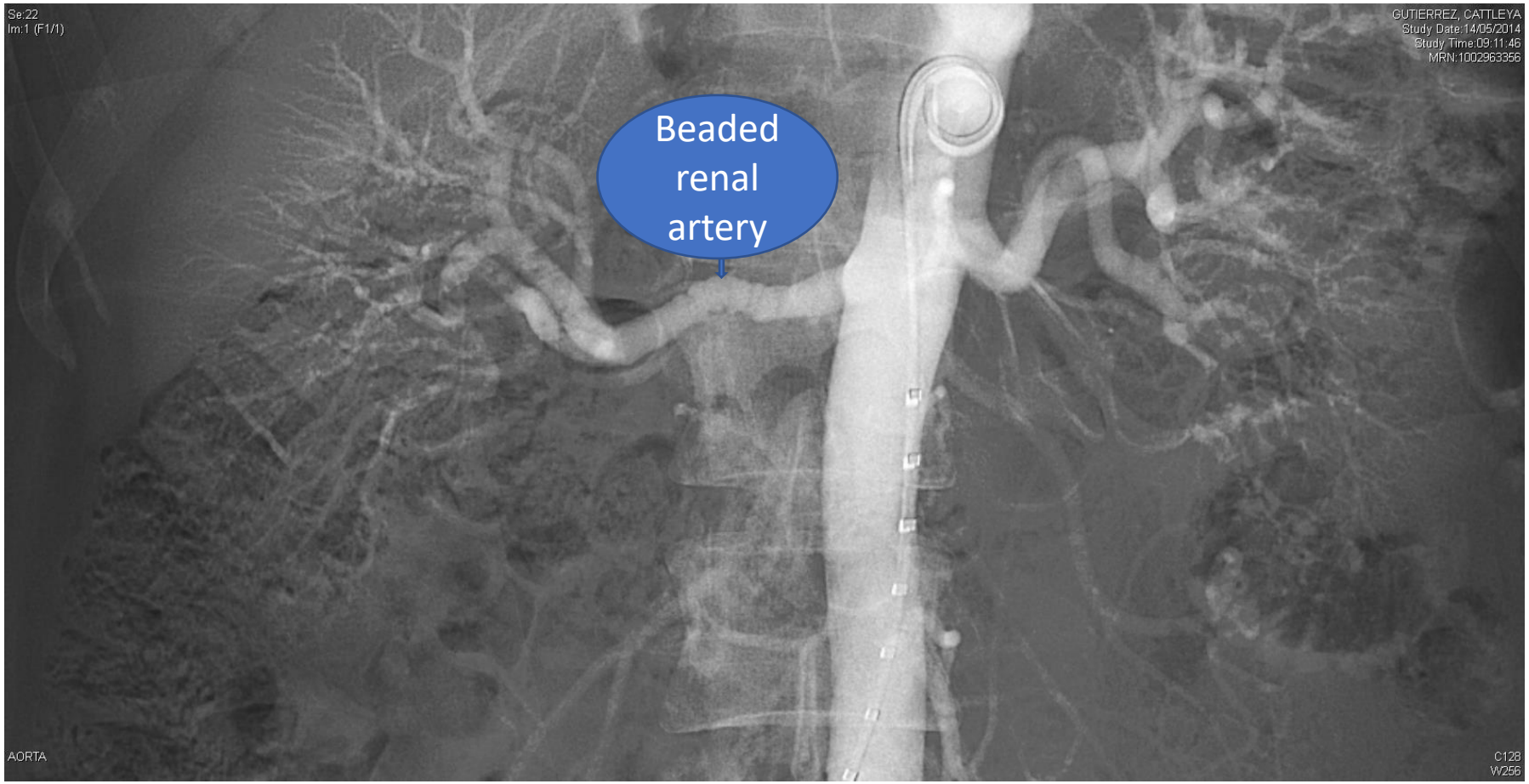
Is revascularisation a must?

- For patients with atherosclerotic RAS, revascularization procedures have not been shown to confer clinical benefit when compared to medical therapy BUT are often considered useful in patients with FMD
- Revascularization should be offered to those with:
  - **short duration of blood pressure elevation**
  - **failure or intolerance to medical therapy**
  - **recurrent flash pulmonary oedema**
  - **unexplained renal failure**

A patient with FMD

- A 32 years old lady with long standing HTN on multiple anti-HTN medications conceived by IVF
- Referred to nephrologist for poorly controlled BP- had right sided abdominal bruit
- CTA- stenosed and beaded appearance of the right renal artery and diagnosed FMD
- Pregnancy ended with a bad outcome
- Had angioplasty and now on less/smaller doses of anti- HTN medications
- LESSONS LEARNT FROM THIS CASE??

FMD right renal artery beaded appearance



Drugs

- OCP
- NSAID
- Synthetic steroids (prednisolone and dexamethasone)
- Nasal decongestants (pseudoephedrine and phenylephrine)
- Calcineurin inhibitors (cyclosporine and tacrolimus)
- Recombinant human erythropoietin
- Illicit drugs :amphetamines and cocaine

Cushing Syndrome

- **Important**: none of the commonly described features like obesity, menstrual irregularities or glucose intolerance are very specific
- **Commonest cause**: prescribed oral prednisolone but inhaled, topical or injected corticosteroids can also be causative

Q. Time: Which of the following is the commoner cause of Cushing syndrome?

a. Adrenal adenoma
b. Adrenal carcinoma
c. Cushing Disease (Cushing syndrome due to increased pituitary secretion of ACTH)
d. Ectopic ACTH secretion

Causes of Cushing Syndrome(remember steroid use is biggest cause)

ACTH dependent causes (up to 80% cases)	NON-ACTH dependent causes (20% cases)
Cushing disease: hypersecretion of ACTH by pituitary gland **65 to 70 %of all Cushing's syndrome**	Adrenocortical adenomas and carcinomas **18 to 20 % of all cases**
Ectopic ACTH secretion by non-pituitary tumours e.g. by bronchial carcinoid, small cell Ca lung etc. **10 to 15% of all cases**	bilateral adrenal micronodular or macronodular hyperplasia **< 2% of all cases**

Cushing Syndrome work up

- **Initial screening** : at least 2 of the following 3 tests should be positive to establish diagnosis

  - mid-night salivary cortisol

  - 24-hours urinary cortisol

  - low-dose dexamethasone suppression test

- If positive follow up with serum ACTH levels
- Low ACTH- CT scan adrenal gland
- *Normal to high ACTH- Is the ACTH from pituitary or an ectopic source??*

Cushing Syndrome with normal to high ACTH

- **High dose Dexamethasone Test:**8 mg dexamethasone given orally at 11 PM will supress ACTH by feedback inhibition and lower cortisol next day in Cushing's disease (pituitary derived ACTH)

NOTE- Ectopic ACTH is completely resistant to negative feedback by dexamethasone

- **MRI pituitary gland** :if above positive
- In equivocal cases **petrosal venous sinus catheterisation** to demonstrate central-to-peripheral ACTH gradient
- Ectopic ACTH-secreting tumours**: CT, MRI, positron emission tomography [PET] or octreotide scintigraphy**

Pheochromocytoma

- Catecholamine-secreting tumours that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia
- Uncommon condition; <0.2% of patients with HTN
- **Rule of 10**: 10% extra-adrenal, multiple, malignant
- Presentation:

- Triad: episodic headache, sweating and tachycardia (50% paroxysmal HTN)

- Incidental finding of adrenal tumour in a hypertensive

- family history of pheochromocytoma or predisposing genetic syndrome (about 40%) namely von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2) and less commonly, neurofibromatosis type 1 (NF1)

NOTE: More likely to be bilateral or recurrent in familial cases

Pheochromocytoma….how do I diagnose?

- Plasma fractionated metanephrines
  - sensitivity : 96 to 100 %
  - specificity : 85 to 89%
- 24 hours urinary fractionated metanephrines and catecholamines
  - sensitivity : 98 %
  - specificity : 98 %
- Plasma fractionated metanephrines is 1st line test when high index of suspicion
- Urinary fractionated catecholamines and metanephrines 1st line test in lower index of suspicion

Risk stratification

- **Low**— 24-hour urinary fractionated catecholamines and metanephrines 1st line :

  - Resistant hypertension
  - Hyperadrenergic spells (palpitations, sweating, headache, tremor, or pallor)

- **High risk for pheochromocytoma** —Plasma fractionated metanephrines 1st line:

  - A family history of pheochromocytoma or predisposing genetic disorder
  - A history of resected pheochromocytoma.
  - An incidentally discovered adrenal mass that has imaging characteristics consistent with pheochromocytoma (unenhanced CT attenuation >10 HU; marked enhancement with IV contrast medium; high signal intensity on T2-weighted MRI, and/or cystic and haemorrhagic changes)

Pheochromocytoma….how do I localise?

- **CT or MRI of the abdomen and pelvis**: Both CT and MRI are quite sensitive (98-100 %), but only 70 %specific because of the high prevalence of adrenal "incidentalomas”
- **123-I-metaiodobenzylguanidine (MIBG) scintigraphy**: If CT/MRI negative in the presence of strongly positive biochemical evidence as MIBG is a compound resembling norepinephrine that is taken up by adrenergic tissue
- **Fludeoxyglucose-positron emission tomography (FDG-PET)**

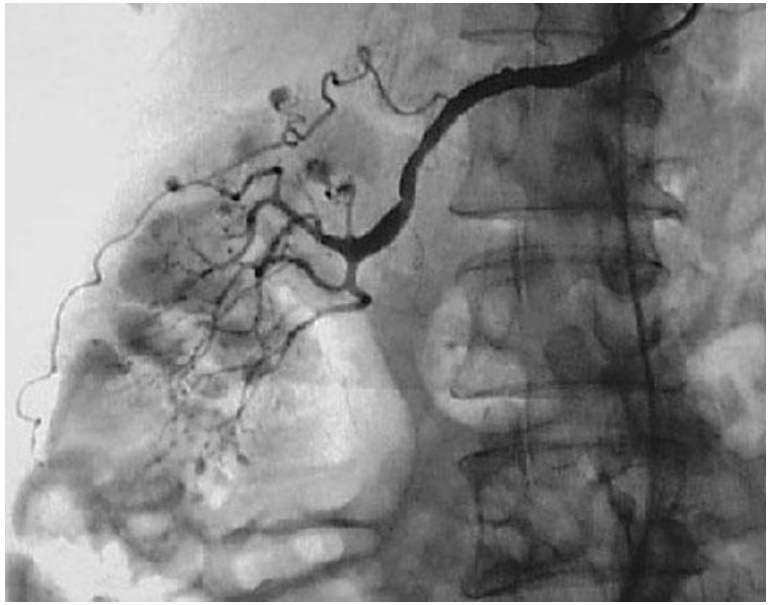
Polyarteritis Nodosa (PAN)

- Vasculitis that typically affects medium-sized muscular arteries with new onset HTN seen in up to 35% of the cases
- Kidneys, skin, joints, muscles, nerves, and gastrointestinal tract most commonly effected
- 20% of the patients are positive for hepatitis B
- Necrosis of arterial wall with disruption of the elastic lamina leads to characteristic development of **aneurysmal dilations and constrictions**

Manifestation	Frequency
Systemic symptoms-fever, malaise, weight loss	80%
Neuropathy- Mononeuritis multiplex, polyneuropathy	75%
Arthralgias and/or myalgias	60%
Skin- Livedo reticularis, purpura, ulcers	50%
Renal failure but typically no glomerulonephritis	50%
Gastrointestinal symptoms- Pain, rectal bleed	40%
New onset hypertension	35%
Orchitis- Testicular pain, swelling	20%
Hepatitis B positive	20%

PAN diagnosis

- ESR,CRP and hepatitis screen with biopsy of affected organ if possible
- CTA and MRA of the renal and mesenteric vessels often diagnostic : multiple aneurysms and irregular constrictions of arteries



Takayasu Arteritis

- Women affected in 80 to 90% of cases and Asians more effected
- Age of onset usually between 10 to 40 years
- Absent or diminished and asymmetric radial pulses and limb claudication
- Abdominal aorta effected eventually in 50%
- **Renal involvement:** Involvement of the renal arteries leads to renovascular hypertension in > 50% cases

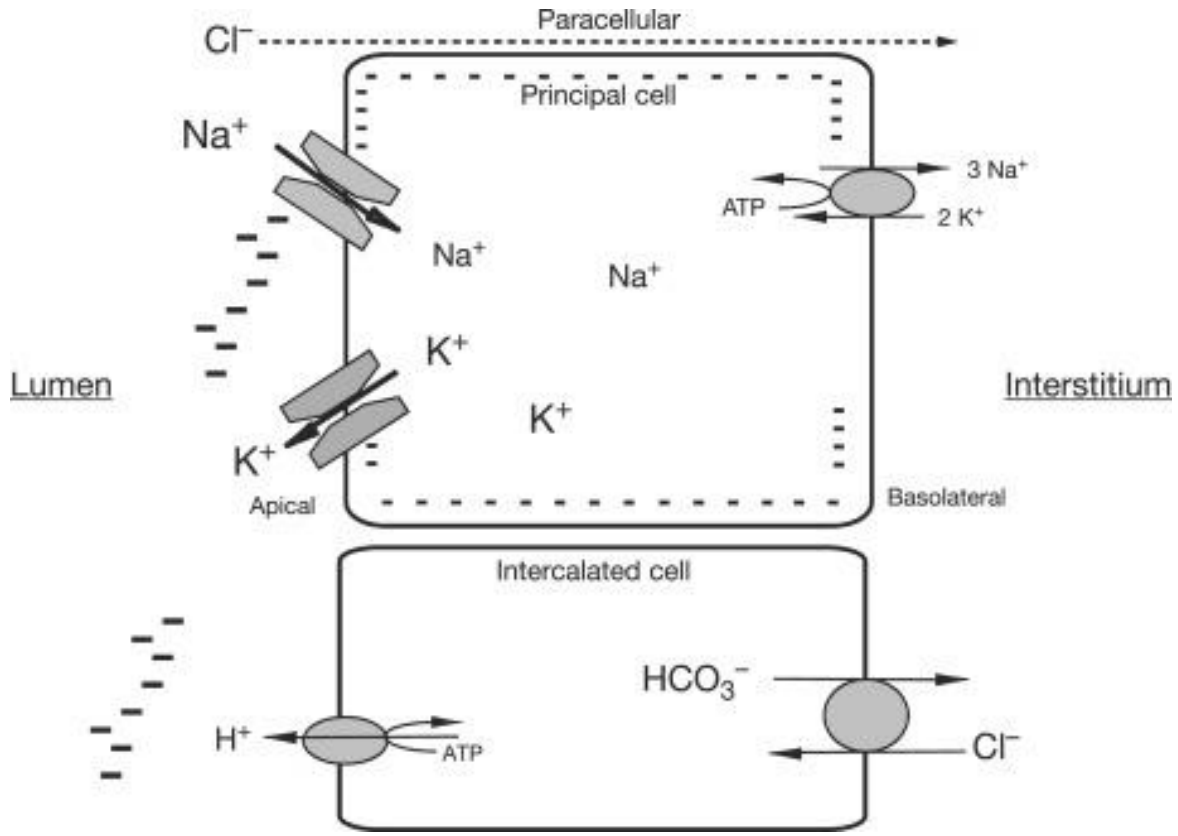
Conditions other than primary aldosteronism leading to HTN with metabolic alkalosis and hypokalaemia

- Liddle Syndrome
- Chronic liquorice ingestion
- Apparent mineralocorticoid excess (AME)
- Glucocorticoid remediable hypertension

Liddle Syndrome

- Autosomal dominant condition with mutation in the ENAC channel (sodium reabsorbing channel in the collecting duct under control of aldosterone) rendering it resistant to normal degradation
- Persistent sodium reabsorption and resultant hypertension
- Presentation at young age and may develop hypokalaemia with metabolic alkalosis
- Genetic testing diagnostic
- *What is the aldosterone and renin level likely to be in this patient?*

Liddle Syndrome:



- HTN with hypokalemia, alkalosis and low renin and low aldosterone

Apparent mineralocorticoid excess (AME)

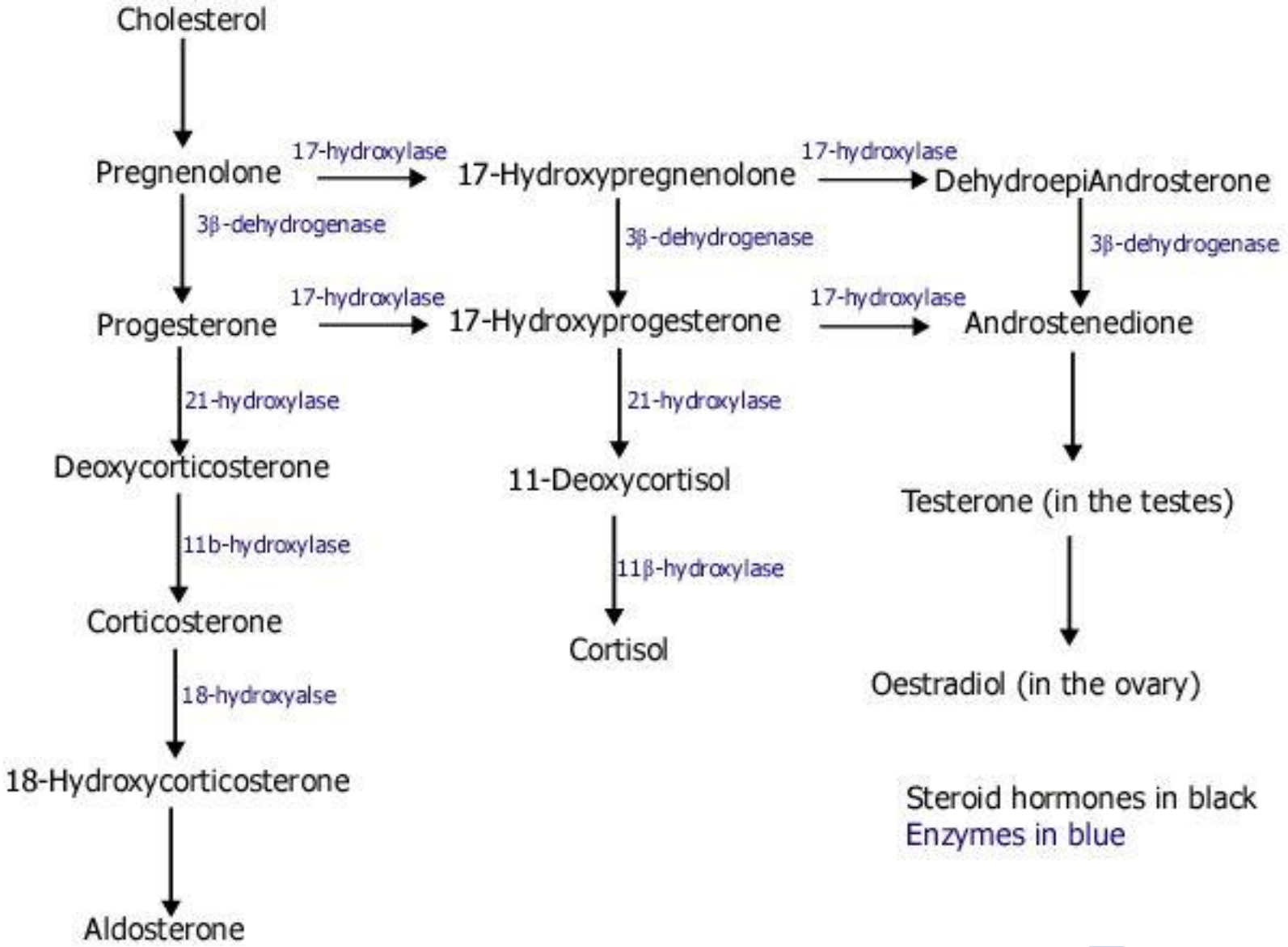
- Cortisol binds as avidly as aldosterone to the aldosterone receptor
- Plasma cortisol concentration >>> aldosterone concentration
- In kidney 11-beta-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2) converts cortisol to the inactive cortisone
- Deficiency of 11-beta-HSD2 leads to elevated levels of cortisol in the kidneys which simulates hyperaldosteronism
- Both plasma aldosterone levels and plasma renin activity low
- 24 hours urine collection reveals abnormally high urine cortisol to cortisone levels

Chronic liquorice ingestion

- Liquorice contains glycyrrhetinic acid, which inhibits 11-beta-HSD2, the same enzyme that is deficient in AME
- As little as 50 g daily for two weeks can produce a rise in blood pressure in normal people
- Urinary free cortisone and cortisol levels may help make the diagnosis, but such testing is not necessary if a history of liquorice ingestion has been obtained

Glucocorticoid–remediable aldosteronism (GRA)

- While both cortisol and aldosterone are synthesised and secreted from the adrenal cortex, only the former is under the control of adrenocorticotrophic hormone (ACTH)
- Mutation of 11-beta-hydroxylase causes both cortisol and aldosterone synthesis to be controlled by ACTH
- Plasma aldosterone elevated and plasma renin activity suppressed, though the aldosterone-renin ratio is typically not as high as with primary aldosteronism


Cholesterol
Pregnenolone
17-hydroxylase
17-Hydroxypregnenolone
17-hydroxylase
DehydroepiAndrosterone
3β-dehydrogenase
3β-dehydrogenase
3β-dehydrogenase
Progesterone
17-hydroxylase
17-Hydroxyprogesterone
17-hydroxylase
Androstenedione
21-hydroxylase
21-hydroxylase
Deoxycorticosterone
11-Deoxycortisol
Testerone (in the testes)
11b-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol
Oestradiol (in the ovary)
18-hydroxyalse
18-Hydroxycorticosterone
Aldosterone
Steroid hormones in black
Enzymes in blue

Thank you

‘The fact that an opinion is widely held is no evidence whatever that it is not utterly absurd’

Bertrand Russell