

Briefly discuss all the following

- a) The Aldosterone to Renin ratio (ARR)
- b) Apparent mineralocorticoid excess
- c) Glucocorticoid suppressible primary hyperaldosteronism

a) The Aldosterone to Renin ratio (ARR)

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Who?

- Moderate to severe hypertension.
- Resistant hypertension.
- Hypertension with spontaneous or diuretic induced hypokalaemia.
- Hypertension with adrenal incidentaloma.
- Hypertension with F/H of early onset of hypertension or CVA under the age of 40.
- All hypertensive 1st degree relatives of patients with PA.

How?

- Ratio of plasma aldosterone conc.(PAC) to plasma rennin level: ARR is the most reliable screening test.
- Appropriate cutoffs depend on method, and based on whether PAC, PRA, DRC, are measured in SI or conventional units
- Accuracy of ARR mainly depends on Renin assay
- Renin Levels measured by Plasma Renin Activity (PRA) or Direct Renin Concentration (DRC)
- Relative lack of precision of PRA at low levels as seen in PA.
- Different detection limits of different commercial PRA assays.

Problems

- Different methods and different units to measure PRA and Aldosterone levels.
- Weak inter-laboratory reproducibility.
- Different cut off values for ARR derived from healthy normotensive volunteers or from retrospective/prospective survey of patient population.
- Large intra individual variability of PAC, PRA and ARR in patients with PA.
- Lack of standardization of testing conditions.
(eg: hypertensive drugs, sodium intake, time of the day for sampling, and postural effects)
- Can be confusing because PRA is halved between the ages of 20 & 60, but aldosterone does not change much

Effect of drugs:

	Aldosterone	Renin
Beta Blockers	↓	↓↓
ACEI & ARBs	↓	↑↑
Ca ²⁺ blockers	→ ↓	↑
Renin inhibitors	↓	↓
Diuretics	↑	↑↑
Alpha-blockers	→	→

False positives: B-blockers
Methyldopa, Clonidine.

False negatives: Diuretics (esp Spironolactone)
 ACE Inhibitors
 Angiotensin-11 blockers
 Calcium Channel blockers

Pre-analytical preparation

- Correct hypokalaemia.
- Unrestricted salt intake before the test.
- Withdraw medications that markedly affect ARR, for at least 4 weeks: Spironolactone, Amiloride, Triamterene, Eplerenone. Potassium wasting diuretics.
- IF results not diagnostic, withdraw other drugs for 2 wks: β blockers, ACEI/ARB, Renin inhibitors, Ca²⁺ blockers, NSAIDS
- If necessary use medication with lesser effect on ARR
- Mid morning sample after patient has been up for at least 2 hrs & is seated for 5-15 min.
- Maintain sample at room temperature (*NOT ON ICE*).
- Immediate transfer to the Lab. for quick centrifugation & rapid plasma freezing pending analysis
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b) Apparent mineralocorticoid excess

Cortisol and aldosterone have the same affinity for the MR (mineralocorticoid receptor) in vitro

In vivo selectivity of Aldosterone for MR is achieved by **11 β -hydroxysteroid dehydrogenase (11 β HSD)** which inactivates cortisol to cortisone and allows aldosterone to occupy MR

11 β HSD deficiency causes build up of intracellular cortisol (usually x 1000 greater than than aldosterone) which occupies MR to cause mineralocorticoid effects:

- Hypertension
- Hypokalaemia
- Low renin
- Low Aldosterone

Increased ratio of urine cortisol-to-cortisone metabolites

{Urinary 11 B-hydroxy metabolites of cortisol are elevated (cortols, tetrahydrocortisol [THF] and C- 19 steroids)

Urinary 11-oxo metabolites are diminished (cortolones and tetrahydrocortisone[THE])}

Also associated with growth retardation/short stature, diabetes insipidus, renal and nephrocalcinosis.

Causes of 11 β HSD deficiency

- Inherited as autosomal recessive
- Inhibitors of 11 β HSD eg liquorice or carbenoxolone
- Ectopic ACTH: high cortisol levels overwhelm 11 β HSD

Treatment

Primary cause

Consists of spironolactone, eplerenone, triamterene, or amiloride

c). Glucocorticoid suppressible primary hyperaldosteronism

AKA familial hyperaldosteronism type I (FH I)

Pathophysiology

- CYP11B1 encodes for 11 β -hydroxylase and its control by ACTH.
- CYP11B2 encodes for Aldosterone synthetase and its control by angiotensin II.
- In GSH: Chimeric Gene (Bits of CYP11B2 with CYP11B1): Gene product synthesises aldosterone that is controlled by ACTH and not Angiotensin II.

Clinical

- Autosomal Dominant
- Hypertension and hypokalaemia
- Resistant hypertension
- Family history
- (Normal growth and development)

Biochemistry

- Hypokalaemia, alkalosis
- Normonatraemia (high normal sodium)
- Inappropriate Kaliuresis

Diagnosis

- Elevated plasma aldosterone
- Low (often suppressed) plasma renin activity
- (High ARR)
- Exaggerated aldosterone response to ACTH
- Increased plasma 18 hydroxycorticosterone and its urine metabolites.
- Chimeric Gene is detectable by molecular biology techniques (100% sensitivity and specificity)

Treatment

- Dexamethasone by suppressing ACTH reduces aldosterone and thus can be used as treatment