# HTN and Disorders of K+

Dr. Surjit Tarafdar

Revise Nephrology

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1. Primary aldosteronism is characterised by-

a) Hypokalaemia
b) Hyperkalaemia
c) Metabolic alkalosis
d) Metabolic acidosis
e) A and C.

# Answer E

Primary hyperaldosteronism should always be suspected in the hypertensive patient with hypokalaemia and metabolic alkalosis (although more than half the patients are normokalemic, but the K is always on the lower side of normal) who is not on thiazide or loop diuretics. Aldosterone leads to reabsorption of $Na^+$ in the CD and the resulting tubular negativity aids in the excretion of $K^+$ and $H^+$.

A 52-year-old woman presents to ED feeling generally unwell. Blood tests reveal metabolic acidosis with a normal anion gap and hypokalaemia. Her urinary pH is 5.7. The rest of the blood tests including phosphate and uric acid are normal.

2. What could have led to this condition?

a) Myeloma
b) Sjogren's syndrome
c) Wilson's disease
d) Diabetes mellitus

3. What is the diagnosis in the above case?

a) RTA type 4
b) RTA type 1
c) RTA type 2
d) RTA type 3

# Answer for 2 & 3: B

The normal anion gap acidosis with hypokalaemia points towards either RTA 1 or 2 but the urinary pH > 5.5 is suggestive of RTA 1 which may be associated with Sjogren's syndrome. Myeloma has a strong association with type 2 RTA.

4. Bartter syndrome is due to a defect in

a) $Na^+$ reabsorption in the distal convoluted tubule
b) $Na^+$ reabsorption in the collecting duct
c) $K^+$ reabsorption in the collecting duct
d) $Na^+$ reabsorption in the ascending limb of loop of Henle

# Answer D

Bartter syndrome is due to defect in $Na^+$ reabsorption in the ascending limb of loop of Henle while defect in $Na^+$ reabsorption in the distal convoluted tubule leads to Gitelman syndrome. A reminder- Bartter and Gitelman syndrome resemble the effects of chronic use of loop and thiazide diuretics respectively.

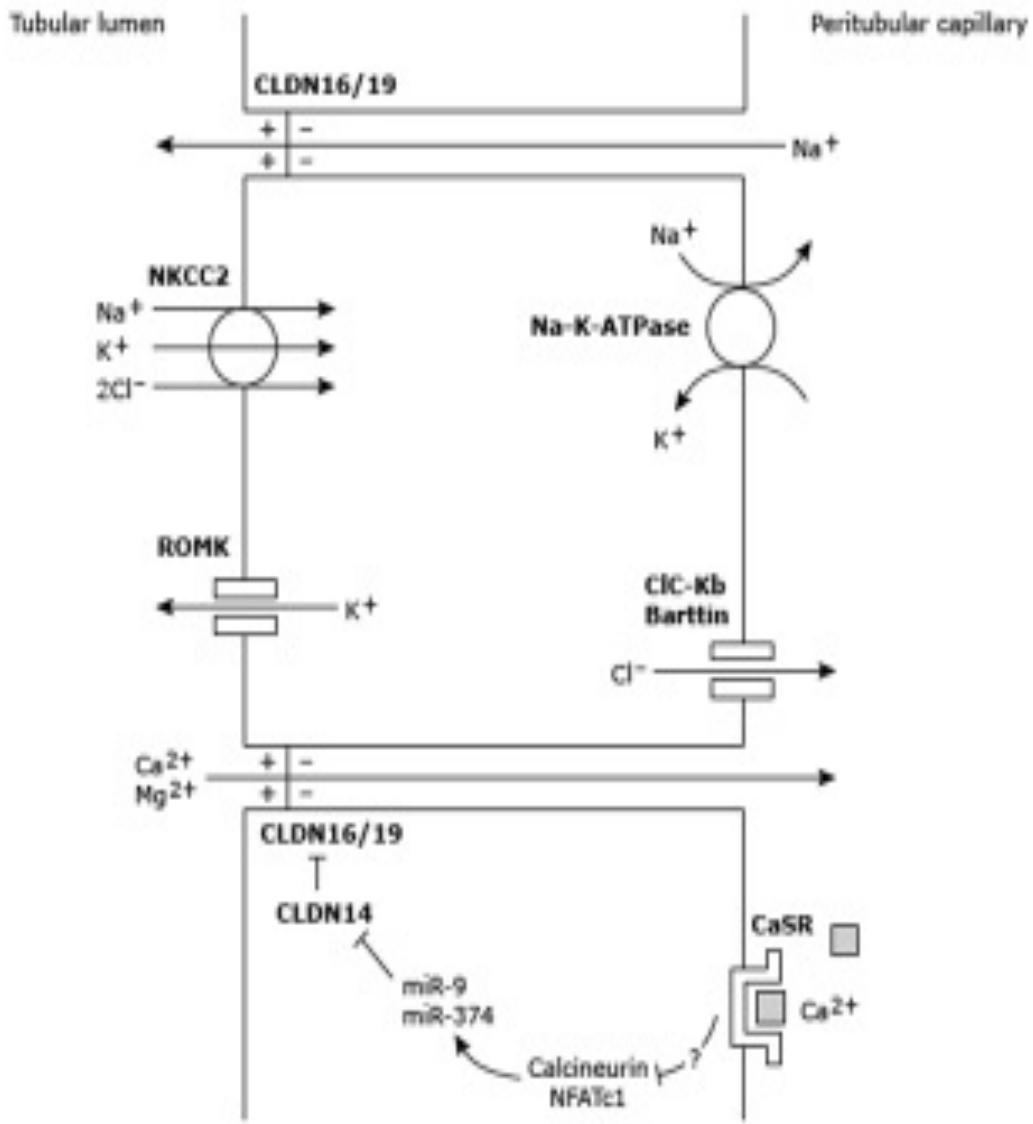
5 Which of the following is true about thiazide diuretics?

a) Can lead to hypercalciuria
b) Can lead to hyperkalemia
c) Can lead to hypocalciuria
d) Can lead to mild metabolic acidosis

# Answer C

Inhibition of $Na^+$ uptake in the distal convoluted tubule by thiazide diuretic leads to volume contraction which in turn leads to increased reabsorption of $Na^+$ in other parts of the tubule. Reabsorption of $Na^+$ by the $Na^+$-$K^+$-$2Cl^-$ cotransporter in the ascending limb of loop of Henle is followed by the back diffusion of the $K^+$ into the tubular lumen while the $Na^+$ and the 2 $Cl^-$ ions diffuse into the peritubular capillary blood.

This creates an electrical gradient with more positivity in the tubular lumen and to neutralise that, $Ca^+$ and $Mg^+$ are reabsorbed via the paracellular cleft. With increased activity of the $Na^+$-$K^+$-$2Cl^-$ cotransporter in response to the volume contraction induced by thiazide diuretic, increased amount of $Ca^+$ is reabsorbed.


Tubular lumen
Peritubular capillary
CLDN16/19
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Na+
NKCC2
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K+
2Cl−
Na+
Na-K-ATPase
K+
ROMK
K+
ClC-Kb
Barttin
Cl−
Ca2+
Mg2+
+
−
+
−
CLDN16/19
CLDN14
miR-9
miR-374
Calcineurin
NFATc1
?
CaSR
Ca2+

6. Chronic liquorice ingestion can lead to-

a) Hyperkalemic metabolic acidosis
b) Hypokalemic metabolic alkalosis
c) Hypokalemic metabolic acidosis
d) Hyperkalemic metabolic alkalosis

## Answer B

In the kidney, 11-beta-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2) converts cortisol to the inactive cortisone, thus preventing cortisol from its natural tendency of binding to the mineralocorticoid receptor. Cortisol has a potent mineralocorticoid action, and the plasma levels of cortisol is significantly higher than that of aldosterone.

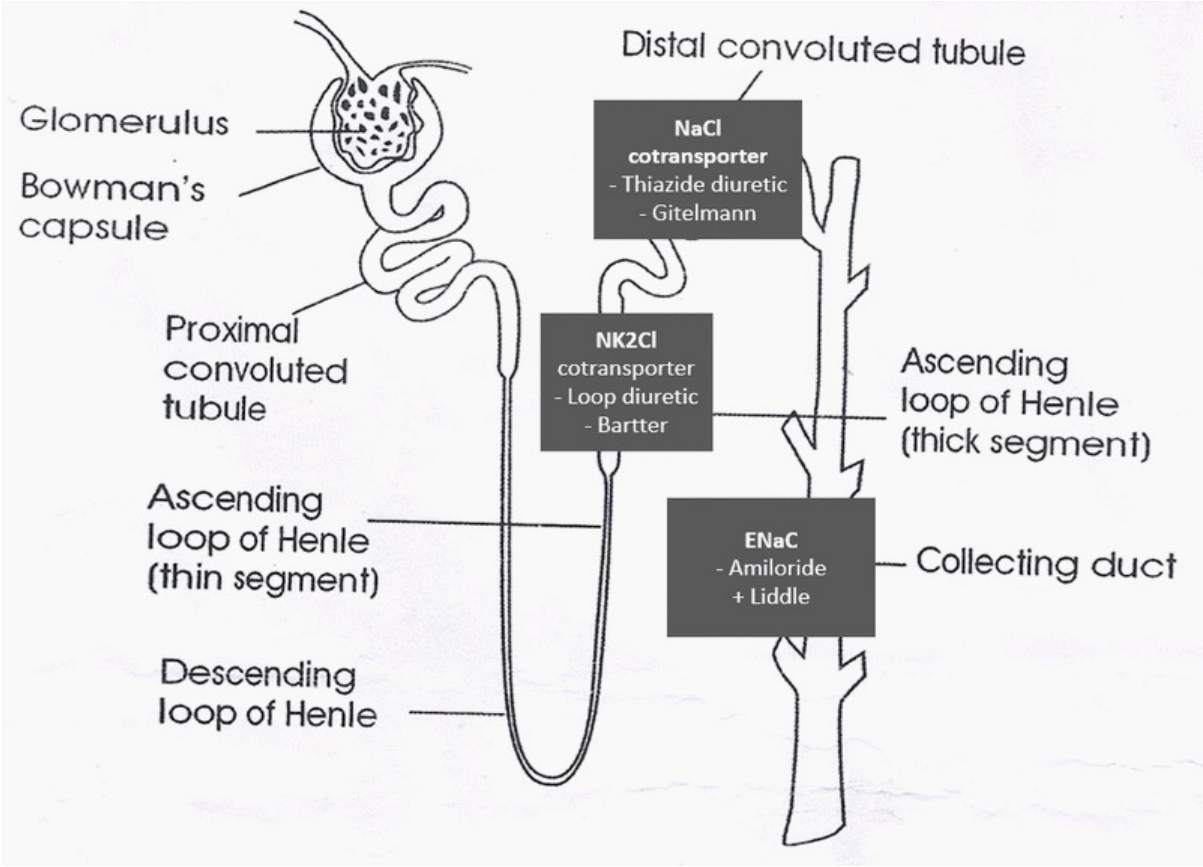
Liquorice contains glycyrrhetinic acid, which inhibits 11-beta-HSD2, the same enzyme that is deficient in the syndrome of apparent mineralocorticoid excess (AME).

Therefore, chronic use of liquorice leads to elevated level of cortisol in the kidneys which in turn leads to exaggerated stimulation of the mineralocorticoid receptor and hypertension with hypokalaemia metabolic alkalosis.

7. A 17-year-old girl who always suffers from extreme thirst and increase urination is found to have metabolic alkalosis with hypokalaemia. A 24-hour urine collection reveals hypercalciuria. What is the most likely diagnosis?

a) Gitelman’s syndrome
b) Liddle’s syndrome
c) Type 1 renal tubular acidosis
d) Bartters syndrome
e) Type 4 renal tubular acidosis

# Diagrammatic representation of Bartter, Gitelman and Liddle syndromes



## Bartter Syndrome

- Defect in $Na^+$ reabsorption in the TAL of loop of Henle
- Normal to increased urinary Ca
- Increased renal vasodilatory prostaglandins
- Treatment: NSAIDs, K supplementation and K-sparing diuretic e.g. spironolactone
- Type III classically grow to adulthood and may develop CKD due to nephrocalcinosis and NSAIDs use
- Often growth and mental retardation

## Gitelman Syndrome

- Defect in thiazide-sensitive $Na^+$-$Cl^-$ cotransporter in DCT
- Low urinary Ca
- Hypomagnesaemia: high urinary Mg loss due to down regulation of $Mg^+$ channel TRPM6
- Treatment: K-sparing diuretic and Mg and K supplementation
- No growth or mental retardation

8. In the context of work up for secondary hypertension, you have diagnosed a patient to have Cushing syndrome. Subsequent investigations revealed a high normal ACTH level. What is the next step now?

a) MRI pituitary gland
b) CT scan of the adrenal gland
c) Low dose dexamethasone test
d) High dose dexamethasone test
e) 24 hours urinary cortisol levels

# Answer D

2 of the following 3 tests should be positive to establish diagnosis of Cushing syndrome.

- Mid-night salivary cortisol
- 24-hour's urinary cortisol
- Low-dose dexamethasone suppression test

Once diagnosis in established, we need to look at the serum ACTH levels. If the ACTH is clearly suppressed, then we scan the adrenal gland. A non-suppressed or high ACTH can mean excess ACTH by the pituitary gland or from an ectopic source and this can be differentiated by-

**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) while ectopically produced ACTH is completely resistant to negative feedback by dexamethasone.

9. Which of the following is the commonest cause of Cushing syndrome?

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

## Answer B

Although iatrogenic Cushing's syndrome is a very common cause of Cushing syndrome, it is seldom reported.

# 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<br>**65 to 70 %of all Cushing's syndrome** | Adrenocortical adenomas and carcinomas<br>**18 to 20 % of all cases** |
| Ectopic ACTH secretion by non-pituitary tumours e.g. by bronchial carcinoid, small cell Ca lung etc.<br>**10 to 15% of all cases** | bilateral adrenal micronodular or macronodular hyperplasia<br>**< 2% of all cases** |

9. For each question, please select the most appropriate option from the list below.

A. Angiotensin converting enzyme
B. Prorenin
C. Renin
D. Angiotensinogen
E. Angiotensin I
F. Angiotensin II
G. Angiotensin receptor
H. Aldosterone

**Question 1**

Synthesised in the liver, and a substrate for renin

**Question 2**

Causes arterial vasoconstriction and sodium reabsorption in the proximal tubule

**Question 3**

Is synthesized in the adrenal glands

Answers:

1. Synthesised in the liver, and a substrate for renin

D. Angiotensinogen

2. Causes arterial vasoconstriction and sodium reabsorption in the proximal tubule

F. Angiotensin II

3. Is synthesized in the adrenal glands

H. Aldosterone

10. 72-year-old man presents with a 3-month history of malaise, arthralgia, abdominal pain, and left foot weakness. In addition to left foot drop, examination reveals that he is hypertensive and has a non-blanching lace-like skin discolouration on his legs.

| Laboratory findings: | Normal values |
| --- | --- |
| ESR 102 mm/hr | [0–15] |
| CRP 68 mg/L | [< 5] |
| Creatinine 120 µmol/L | [45–90] |
| MSU 1+ proteinuria | |

CT scan angiography shows multiple small vessel aneurysms in the renal and mesenteric arteries.

10. What is his autoantibody screening most likely to show?

a) c-ANCA.
b) dsDNA autoantibodies.
c) No autoantibodies detected.
d) p-ANCA.
e) Rheumatoid factor

# Answer C. No autoantibodies detected

- This patient has PAN as suggested by the multisystem involvement and characteristic imaging.
- PAN is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries. The characteristic absence of involvement of veins and smaller arteries or capillaries, and ANCA negativity, helps to differentiate PAN from some of the other vasculitis. The aetiology and pathogenesis of PAN are unknown, but there is a strong association with hepatitis B suggesting that circulating immune complexes might localise on vessel walls causing the condition. Histologically, PAN is characterised by segmental transmural fibrinoid necrosis of arteries accompanied by infiltrating leucocytes and lack of granulomas.
- More than 80% patients have non-specific systemic complaints such as fever and weight loss. Peripheral neuropathy, typically in the form of mononeuritis multiplex, is seen in up to three quarters of patients. Almost half of patients have gastrointestinal involvement presenting as abdominal pain or blood in the stool. Kidney involvement may lead to infarction or haemorrhage which may present with flank pain and haematuria. Up to one third of patients develop hypertension while 20% of patients may present with testicular pain due to orchitis.

There is no single diagnostic test for PAN. Acute phase reactants like ESR and CRP are often elevated and up to one third of patients are hepatitis B positive. While a tissue biopsy should be done where possible, a mesenteric or renal angiogram in the setting of a suggestive history and clinical presentation is often diagnostic. The angiogram characteristically shows multiple aneurysms and irregular constrictions in the larger vessels with occlusion of smaller penetrating arteries

Table: Clinical presentation of PAN

| | |
|---|---|
| **Systemic features- fever/malaise** | **80%** |
| **Peripheral Neuropathy** | 75% |
| **Arthralgia/myalgia** | 60% |
| **Skin- livedo reticularis, purpura** | 50% |
| **Kidney- infarction or haemorrhage** | 50% |
| **GI- abdominal pain, blood in stool** | 40% |
| **Hypertension** | 35% |
| **Orchitis** | 20% |
| **Stroke** | 20% |
| **Cardiac-cardiomyopathy, pericarditis** | 10% |

11. The prevalence of adrenal incidentaloma can be as high as 10% in the elderly population. Which of the following statements is incorrect about this condition?

a) Adrenocortical carcinomas are significantly associated with mass size, with 90 percent being more than 4 cm in diameter
b) A homogeneous adrenal mass with a smooth border, diameter< 4 cm and an attenuation value <10 HU on unenhanced CT is very likely to be a benign adenoma
c) Phaeochromocytomas which are generally benign (>90%) have low attenuation on unenhanced CT i.e., <10 HU
d) Benign adenomas have a rapid contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of more than 50 percent)
e) Phaeochromocytomas may have variable size and may be bilateral.

# Answer C

An adrenal incidentaloma is defined a mass lesion greater than 1 cm in diameter, serendipitously discovered by radiologic examination.

Phaeochromocytomas which are generally benign (>90%) have  high attenuation on unenhanced CT  i.e., >20 HU. They also tend to have variable size. They are more likely to be bilateral (25% than the usual 10%) when associated with familial syndromes such as MEN2, NF1 and VHL syndrome.

**Typical imaging features** — The imaging characteristics of adrenal masses are summarized here.

**Benign adenomas**

- Round and homogeneous density, smooth contour, and sharp margination
- Diameter less than 4 cm, unilateral location
- Low unenhanced CT attenuation values (≤10 HU)
- Rapid contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of more than 50 percent)

**Pheochromocytomas**

- Increased attenuation on unenhanced CT (>20 HU)
- Increased mass vascularity
- Delay in contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of less than 50 percent)
- High signal intensity on T2-weighted MRI
- Cystic and haemorrhagic changes
- Variable size and may be bilateral

**Adrenocortical carcinoma**

- Irregular shape
- Inhomogeneous density because of central areas of low attenuation due to tumour necrosis
- Tumour calcification
- Diameter usually >4 cm
- Unilateral location
- High unenhanced CT attenuation values (>20 HU)
- Inhomogeneous enhancement on CT with intravenous contrast
- Delay in contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of less than 50 percent)
- Hypointensity compared with liver on T1-weighted MRI and high to intermediate signal intensity on T2-weighted MRI

**Adrenal metastases**

- Irregular shape and inhomogeneous nature
- Tendency to be bilateral
- High unenhanced CT attenuation values (>20 HU) and enhancement with intravenous contrast on CT
- Delay in contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of less than 50 percent)
- Isointensity or slightly less intense than the liver on T1-weighted MRI and high to intermediate signal intensity on T2-weighted MRI (representing an increased water content)

12. A 50-year-old man with no previous medical history apart from hypertension is diagnosed to have pheochromocytoma in the context of work-up for an adrenal incidentaloma. What would be the best treatment option for him?

a. Lifelong alpha blockers

b. Lifelong beta blockers

c. Immediate surgical resection of the tumour

d. Lifelong combination of alpha and beta blockers

e. Alpha blockers followed by addition of beta blockers followed by surgery

# Answer E

Once a pheochromocytoma is diagnosed, all patients should undergo a resection of the pheochromocytoma following appropriate medical preparation. Preoperative medical therapy is aimed at:

- Controlling hypertension (with alpha blockers) and tachycardia (with beta blockers)
- Volume expansion to counter the catecholamine induced volume contraction

**Alpha-adrenergic blockade** — An alpha-adrenergic blocker is given for at least 7 days preoperatively to normalize blood pressure and expand the contracted intravascular space. With their more favourable side-effect profiles and lower costs, selective alpha-1-adrenergic blocking agents e.g., prazosin or terazosin, are often used rather than the traditional long acting alpha blocker phenoxybenzamine.

**High sodium diet** — On the second or third day of alpha-adrenergic blockade, patients are encouraged to start a diet high in sodium content (>5000 mg daily) because of the catecholamine-induced volume contraction and the orthostasis associated with alpha-adrenergic blockade. This degree of volume expansion may be contraindicated in patients with congestive heart failure or renal insufficiency.

**Beta-adrenergic blockade** — After adequate alpha-adrenergic blockade has been achieved, beta-adrenergic blockade is initiated, which typically occurs two to three days preoperatively. The beta-adrenergic blocker should **never** be started first because blockade of vasodilatory peripheral beta-adrenergic receptors with unopposed alpha-adrenergic receptor stimulation can lead to a further elevation in blood pressure.

13.Which of the following patient’s serum aldosterone level would NOT be high?

a. Patient with RAS

b. Patient with FMD

c. Patient on thiazide diuretic

d. Patient with primary aldosteronism

e. Patient with Liddle syndrome

## Answer E

Patients with renovascular HTN (includes RAS and FMD) have increased renin secretion due to low blood flow to the kidney and the subsequently increased aldosterone levels.

Patients on thiazide and loop diuretics are volume contracted (due to the diuresis) and as a result, have activated RAS and the consequent secondary aldosteronism. Let us revise Liddle syndrome.

Patients with Liddle syndrome have low renin as well as aldosterone levels.

### 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?*