TUBULOPATHIES

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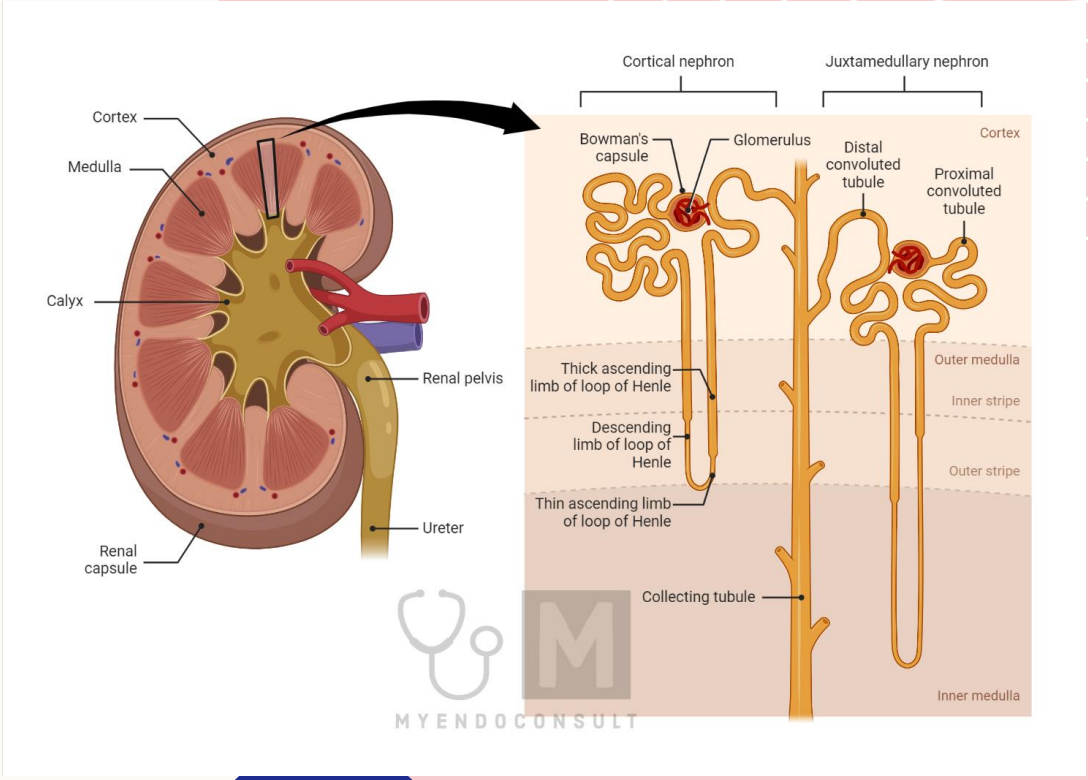
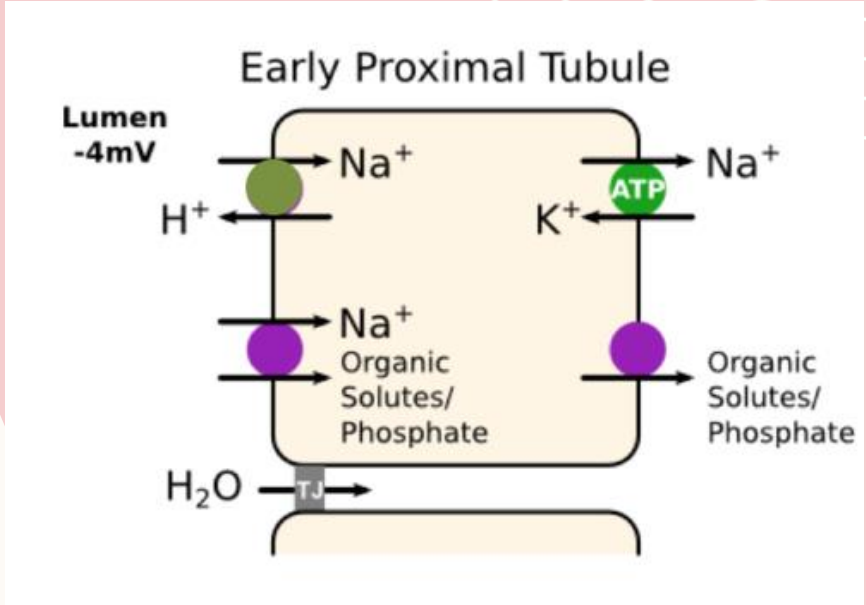
OVERVIEW OF RENAL TUBULAR ANATOMY AND FUNCTION



EARLY PROXIMAL CONVOLUTED TUBULE

- Reabsorbs all glucose and amino acids and most of the bicarbonate, sodium, chloride, phosphate, potassium and water, via isotonic reabsorption.
- Sodium is reabsorbed by cotransport with **glucose**, **amino acids**, phosphate, and lactate.



LATE PROXIMAL CONVOLUTED TUBULE

- Filtered glucose, amino acids, and bicarbonate have already been completely removed from the tubular fluid by reabsorption in the early proximal tubule.
- In the late proximal tubule, sodium is reabsorbed with chloride, either trans-cellularly, or paracellularly.

THIN DESCENDING LOOP OF HENLE

- Also called the concentrating segment, as it makes urine hypertonic.
- This is achieved by passively reabsorbing water via medullary hypertonicity (impermeable to sodium).

THICK ASCENDING LOOP OF HENLE

- Also called the diluting segment, as it makes urine hypotonic (impermeable to water).
- It contains a Na-K-2Cl cotransporter which is responsible for their reabsorption.
- It also indirectly induces paracellular reabsorption of magnesium and calcium through positive lumen potential generated by K+ back leak.
- Site of action for loop diuretics.

EARLY DISTAL CONVOLUTED TUBULE

- Like the TAL, it is also impermeable to water and makes the urine more hypotonic. It is called the cortical diluting segment.
- It contains a Na-Cl cotransporter which is responsible for their reabsorption.
- Site of action for thiazide diuretics.

LATE DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

Two types of cells:

1. Principal cells:

- Reabsorbs Na+ and H2O.
- Secrete K+.
- Aldosterone increases Na+ reabsorption and increases K+ secretion.
- Antidiuretic hormone (ADH) increases H2O permeability by directing the insertion of H2O channels (aquaporin) in the luminal membrane. In the absence of ADH, the principal cells are virtually impermeable to water.
- Site of action of potassium sparing agents.

LATE DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

2. Intercalated cells:

- Secrete H+ by an H+ -adenosine triphosphatase (ATPase), which is stimulated by aldosterone.
- Reabsorb K+ by an H+,K+ -ATPase.

TUBULOPATHIES

Kidney tubules are responsible for the preservation of fluid, electrolyte and acid-base homeostasis via passive and active mechanisms. These physiological processes can be disrupted by inherited or acquired etiologies. The net result is a tubulopathy.

- The clinical presentation of a tubular dysfunction is non-specific.
- Prominent feature of tubular dysfunction in children and young adults include polyuria, polydipsia, irritability, **growth failure**, nephrocalcinosis and blood pressure abnormalities.
- It is important to make a prompt and accurate diagnosis of tubulopathies in children and young adults. This allows timely and appropriate management, including disease-specific therapies, and avoids serious complications such as growth failure.
- It is essential to utilize observed biochemical changes to localize which tubular segment is implicated.

INITIAL INVESTIGATIONS

- Biochemical profile (Na, K, Cl, HCO_3, urea, creatinine, Ca, Mg and PO_4).
- Venous Blood Gas.
- Renin/ aldosterone levels.
- Urine dipstick for glucose.
- Urine microscopy.
- Urine protein: creatinine ratio.
- Urine calcium: calcium ratio.
- Urine osmolality.
- Kidney ultrasound.

CLASSIFICATION OF TUBULOPATHIES

- Hypokalemic Metabolic Acidosis:
  - ❖ Proximal tubular bicarbonate wasting:
    - ❑ Proximal Renal Tubular Acidosis (RTA type 2).
    - ❑ Fanconi syndrome.
  - ❖ Impaired hydrogen excretion in the distal tubules:
    - ❑ Distal Renal Tubular Acidosis (RTA type 1).

- Hyperkalemic metabolic acidosis:
  - ❖ RTA type 4.
- Hypokalemic metabolic alkalosis with hypotension/ normotension:
  - ❖ Bartter syndrome.
  - ❖ Gitelman syndrome.
- Hypokalemic metabolic alkalosis with hypertension:
  - ❖ Primary hyperaldosteronism.
  - ❖ Liddle syndrome.

RENAL TUBULAR ACIDOSIS

It is a clinical syndrome of disordered renal acidification in which the kidney fails to maintain a normal plasma concentration of bicarbonate.

HYPERKALEMIC METABOLIC ACIDOSIS

RTA TYPE 4

- Etiology: Usually due to either aldosterone deficiency or tubular resistance to the action of aldosterone, called pseudo-hypoaldosteronism
- Hypoaldosteronism in children is more likely to be due to drugs that impair aldosterone release or function, such as: heparin, NSAID, trimethoprim and spironolactone.
- Other causes include CKD, adrenal insufficiency and autoimmune disorders.
- Psuedohypoaldosteronism is most common to be secondary to urosepsis and it’s reversible.
- The different causes of hypoaldosteronism can be differentiated by measurement of plasma renin activity (PRA), serum aldosterone, and serum cortisol.

FEATURES

- In RTA type 4, hyperkalemia distinguishes this form from types I and II.
- Other clinical features in children with hypoaldosteronism may include failure to thrive and hyponatremia because of sodium loss.
- Urine pH is less than 5.5.
- Nephrolithiasis is usually absent.
- **HYPERKALEMIC METABOLIC ACIDOSIS.**

MANAGEMENT

1. Chronic treatment for hyperkalemia with sodium potassium exchange resin.
2. Fludrocortisone.
3. Restricting potassium intake.
4. Using diuretics that increase potassium loss and stop potassium sparing drugs.

HYPOKALEMIC METABOLIC ACIDOSIS

DISTAL RENAL TUBULAR ACIDOSIS (RTA TYPE 1)

- Distal RTA results from the inability of α-intercalated cells to secrete hydrogen.
- Progressive hydrogen ion retention leads to a fall in plasma bicarbonate concentration.

CAUSES

1. Primary: Either sporadic or inherited:

- Marfan syndrome.
- Wilson syndrome.
- Ehlers-Danlos syndrome.
- Familial hypercalciuria.

CAUSES

2. Secondary:

- Interstitial nephritis.
  - Pyelonephritis.
  - Sickle cell nephropathy.
- Obstructive uropathy.
- Vesicoureteral reflux.
- Amphotericin B.
- Lithium.
- Cisplatin.

CLINICAL MANIFESTATIONS

- The recessive genetic forms present in infancy and the dominant form later in life.
- Non-anion gap metabolic acidosis.
- Urinary pH> 5.5, differentiates RTA 1 from other types.
- Hypokalemia.
- Hyperchloremia.
- Hypercalciuria.
- Hypocitraturia.
- Bone disease.
- Failure to thrive (due to electrolyte imbalance).
- Rickets.
- Polyuria
- Polydipsia.
- Weakness/ fatigue.
- Nephrolithiasis.

MANAGEMENT

- The goals of RTA therapy are to improve growth, prevent nephrolithiasis and control any underlying disease process.
- Administration of alkali: 2-3 mEq/kg/day can be administered in any form, although the preferred form is as potassium citrate.
- Correction of acidosis usually corrects the hypokalemia, but K + supplements may be necessary.

PROXIMAL RENAL TUBULAR ACIDOSIS (RTA TYPE 2)

- Referred to as ISOLATED RTA, it is caused by a defect in the proximal tubule absorption of bicarbonate, which leads to bicarbonate wasting.
- Caused by genetic mutation of SLC4A4 variant which encodes for basolateral sodium bicarbonate exchanger.
- Associated with abnormalities such as cataract, glaucoma and band keratopathy.

CLINICAL FEATURES

- Polyuria.
- Polydipsia.
- Dehydration.
- Features of hypokalemia such as muscle weakness and hyporeflexia.

MANAGEMENT

- The mainstay of therapy in all forms of RTA is bicarbonate and electrolyte replacement.
- Hypercalciuria and nephrocalcinosis are managed by adequate intake of fluid and administration of citrate which binds urinary calcium and prevent crystallization.

FANCONI SYNDROME

PATHOPHYSIOLOGY

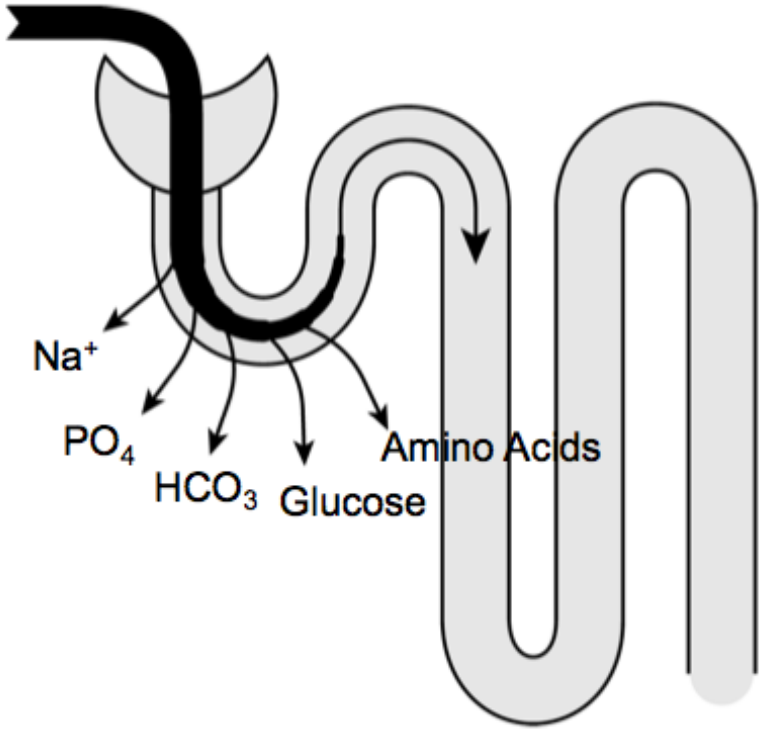
Renal Fanconi Syndrome (RFS) refers to the generalized dysfunction of the of the proximal tubules of the nephron.
Another name for RFS is Generalized Proximal Tubulopathy (GPT).

The proximal tubules of the nephrons are responsible for the resorption of amino acids, glucose, bicarbonate, phosphate, sodium, potassium, low molecular weight proteins, water and uric acid.

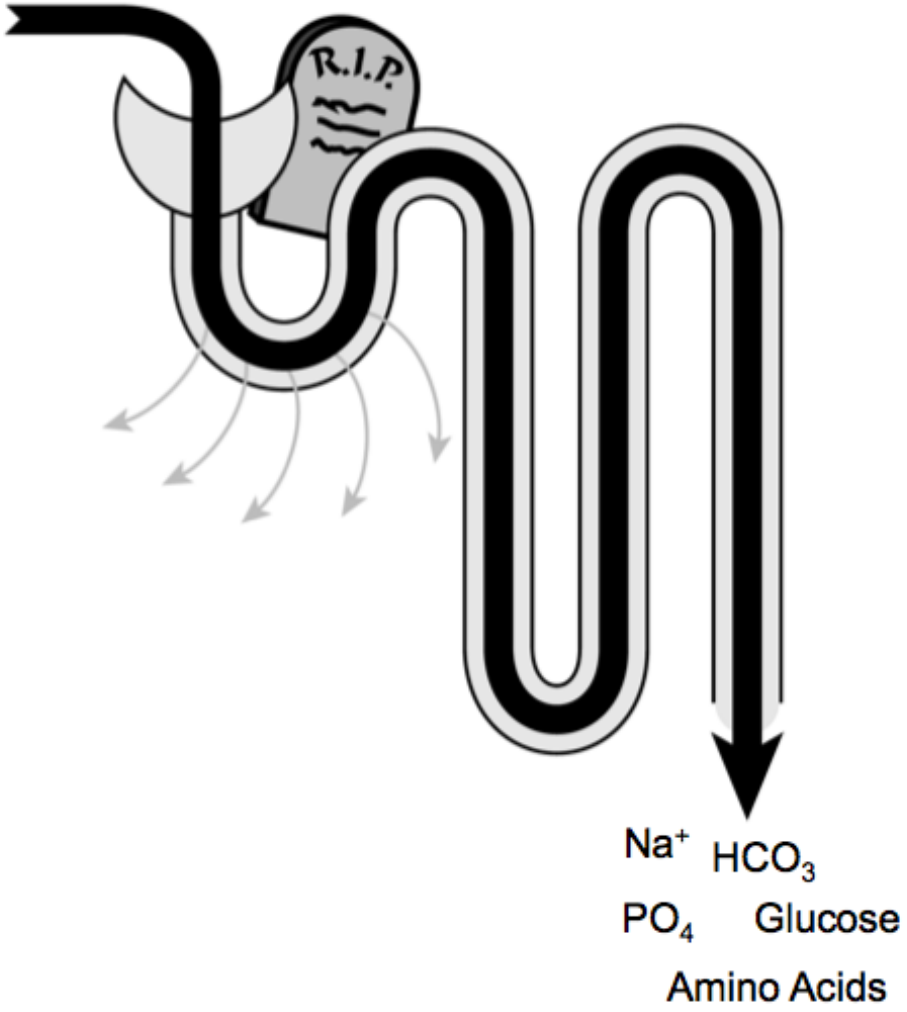
Any proximal tubule dysfunction leads to the failure of resorption of these molecules and thus they are excreted in the urine. This leads to polyuria, glucosuria, LMW proteinuria, aminoaciduria, phosphaturia and hypercalciuria.

The loss of bicarbonate leads to **metabolic acidosis** while the loss of phosphate leads to **hypophosphatemic rickets.**

Proximal Tubule



Fanconi's Syndrome



ETIOLOGY

Most cases are secondary to another condition, such as:

- Cystinosis (most common).
- Wilson’s disease.
- Tyrosinemia.
- Glycogen Storage Disease.
- Galactosemia.
- Lowe syndrome.
- Dent disease.

A minority of cases are primary, caused by a mutation of the Sodium-Phosphatase co-transporter (NaPi-11).

CLINICAL PRESENTATION

The patient may have 1 or more of the following:

- Polyuria and polydipsia, caused by the diuretic effect of glucosuria.
- Rickets, osteomalacia and impaired bone growth, due to hypophosphatemia and it’s effect on vitamin D metabolism.
- Hypotension and muscle weakness, secondary to the sodium and potassium wasting, respectively.
- Failure to thrive.
- Nephrocalcinosis, due to the hypercalciuria.

PHYSICAL EXAMINATION

The patient may have 1 or more of the following:

- Signs of dehydration (dry mucous membranes, loss of skin turgor, slow capillary refill).
- Signs of rickets (bowing of the legs, craniotabes, wide fontanelles, Harrison’s sulcus, rib beading and swelling of the wrists).
- Delayed growth and physical milestones.
- Hepatomegaly (in galactosemia, tyrosinemia and cystinosis).
- Cystine deposits in the cornea.

PRIMARY INVESTIGATIONS

Urinalysis:

- Glucosuria.
- LMW proteinuria.
- Aminoaciduria.
- Phosphaturia.
- Hypercalciuria.

Blood tests:

- Hyponatremia.
- Hypokalemia.
- Hypophosphatemia.
- Hypouricemia.

ABG: Metabolic acidosis, due to the loss of HCO_3.

SECONDARY INVESTIGATIONS

- X-rays to look for any signs of rickets (metaphyseal cupping, splaying and fraying of the wrists, widening of the physis, poor mineralization of the epiphyseal centers).
- Ultrasonography to look for hepatomegaly and nephrocalcinosis.
- Liver biopsy to look for any metabolic disorder (Wilson’s disease, galactosemia, tyrosinemia and glycogen storage disease).
- Slit-lamp examination to look for cystine deposits.
- Serum copper and ceruloplasmin levels.
- Serum galactose.
- Serum tyrosine.

TREATMENT

In an acute setting, we should deal with the dehydration by fluid resuscitation.
After the patient’s state becomes stable, we should manage the electrolyte disturbances with lifelong supplementation of bicarbonate, sodium, potassium, phosphate and vitamin D. This will improve the patient’s metabolic acidosis and rickets.
If the disease is secondary to another illness, the underlying illness should be managed.
The patient may require a kidney transplant on the long run if renal failure develops.
Treat any complication, if present.

CASE EXAMPLE

- A 4-year-old girl presented with an inability to walk, repeated respiratory tract infections and failure to thrive.
- There was no associated vomiting, jaundice, convulsions or photophobia.
- She is the second child to a non-consanguineous couple. Her older sister is 6 years old and is healthy.
- She was born full-term via a natural vaginal delivery at 2.5kgs.
- Despite having a normal dietary intake, she has failed to thrive since birth.
- Her physical milestones are delayed but her mental milestones are normal.

- On physical examination, her weight and length were recorded at 7.5kgs and 76cm (both less than 5th percentile for her age).
- Also noted were an open anterior fontanelle, frontoparietal bossing, a bell-shaped chest with beading of the ribs, Harrison’s sulcus, flaring of the bones at the wrist, double malleoli and bowing of the lower limbs.
- She had marked hypotonia with normal power and reflexes. Her fundus was normal.
- Her abdomen was distended, and the liver was palpable 3cm below the costal margin. Her spleen was not palpable.
- There were bilateral rales on chest auscultation.

Labs:

- Blood Urea Nitrogen (BUN): 8mg/dL [N8-23].
- **Serum Creatinine: 0.1mg/dL [N0.6-1.5].**
- Serum Albumin: 3.8g/dL [N3.5-6].
- Serum Cholesterol: 160mg/dL [N150-250].
- **Serum Sodium: 132 mEq/L [N135-145].**
- Serum Potassium: 3.8 mEq/L [N3.5-5.5].
- Serum Chloride: 105 mEq/L [N95-105].
- **Serum Calcium: 6.8mg/dL [N8.8-11].**
- **Serum Uric Acid: 1mg/dL [N2-7].**
- **Serum Phosphate: 1.5mg/dL [N4-7].**
- **Alkaline Phosphatase: 2100IU/L [N57-180].**
- AST: 26IU/L [N5-40].
- ALT: 47IU/L [N5-45].
- **ABG revealed a persistent metabolic acidosis with bicarbonate ranging from 11-13 mEq/L and pH from 7.22-7.27 with a simultaneous urinary pH of 5.5.**
- Fasting Blood Sugar: 75mg/dL [N65-110] and a normal OGTT (vital to differentiate between Fanconi syndrome and diabetes mellitus).
- Serum ceruloplasmin levels were within normal limits.
- Hemoglobin: 11.4g/dL.
- Mantoux test: Negative.

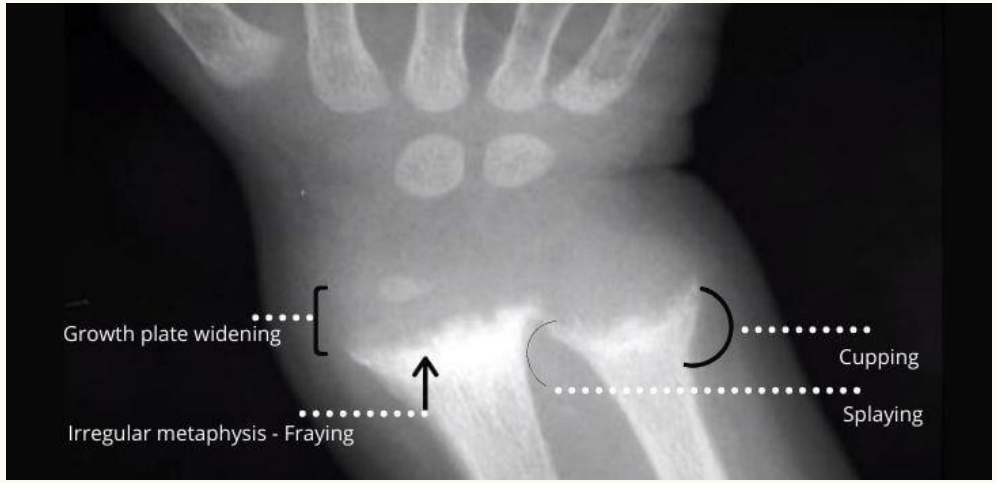
In the hospital, she was found to have polyuria (2L in 24 hours).

Urinalysis:

- Proteinuria of 1+.
- Glucosuria of 4+.
- Aminoaciduria:
  - Alanine.
  - Threonine.
  - Serine.
  - Glutamic Acid.
  - Glycine.
  - Lysine.
- Sodium: 225mmol.
- Potassium: 57mmol.
- Chloride: 165mmol.
- Calcium: 240mg.
- Phosphate: 188mg.
- Uric Acid: 714mg.
- Glucose: 32g.

Imaging:

- X-ray of her wrists revealed florid rickets with cupping, splaying and fraying of the radial and ulnar ends.
- Ultrasonography of the abdomen revealed mild hepatomegaly and normal-sized kidneys, with no evidence of nephrocalcinosis.
- Liver biopsy showed normal liver tissue with no evidence of a storage disorder.
- Slit-lamp examination of her eyes revealed no cystine crystals.



The association of severe growth retardation, resistant rickets, metabolic acidosis, glucosuria, generalized aminoaciduria, hyperuricosuria led to the diagnosis of Fanconi syndrome (Generalized Proximal Tubulopathy).

ETIOLOGY

Secondary causes were excluded by obtaining normal results such as a normal serum ceruloplasmin level, normal liver biopsy, normal OGTT and FBS results.
This makes our patient one of the minorities by having **primary** Fanconi syndrome.

TREATMENT

SODAMINT TABLETS (NAHCO3), AT 8MEQ/KG/DAY, TO TREAT THE DECREASED LEVELS OF HCO3 IN THE SERUM.

JOULE'S SOLUTION (PHOSPHATE RICH) AND VITAMIN D TO TREAT HER HYPOPHOSPHATEMIC RICKETS.

ANTIBIOTICS TO TREAT HER RESPIRATORY INFECTION.

2-MONTH FOLLOW-UP

- ABG showed a pH of 7.36 and a HCO_3 of 20.9mEq/L.
- Serum calcium was 8.9mg/dL.
- Serum phosphate was 5.4mg/dL.
- Alkaline phosphatase was 565IU/L.
- Anterior fontanelle closed.
- Child could now sit up with a straight back.
- Hypotonia improved.
- Weight and height showed no improvement.

HYPOKALEMIC METABOLIC ALKALOSIS WITH HYPOTENSION/ NORMOTENSION

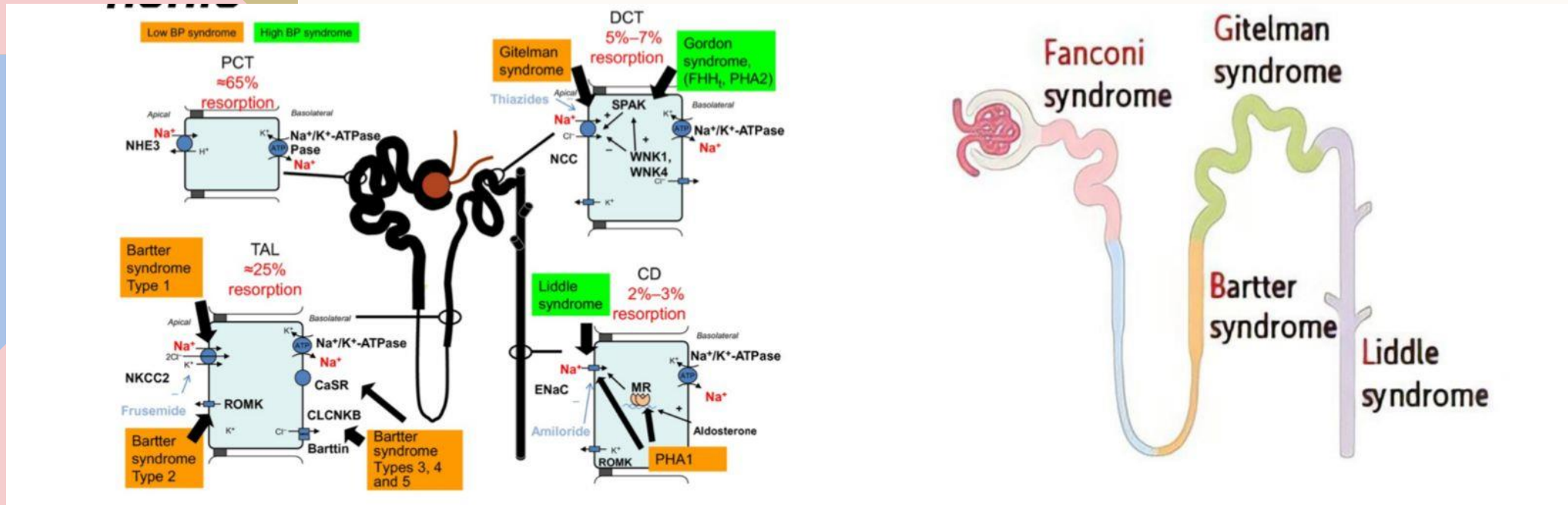
GITELMAN SYNDROME

- Rare, autosomal recessive genetic mutation of sodium chloride cotransporter, leads to sodium and chloride wasting with secondary hyperaldosteronism.
- Children generally present later in life (early childhood or adolescence) with polyuria, polydipsia and hypotension.
- They also present with hypomagnesemia (mechanism unclear) which results in muscle cramps, tetany and chondrocalcinosis.
- GS compensates for the sodium loss by enhancing reabsorption in the proximal tubules, this result in increased paracellular reabsorption of calcium and subsequent hypocalciuria (different than Bartter syndrome).
- Therapy is directed at correcting hypokalemia and hypomagnesemia with supplemental potassium and magnesium.
- Sodium supplementation or treatment with prostaglandin inhibitors is generally not necessary because patients typically do not have episodes of volume depletion or elevated prostaglandin excretion.

BARTTER SYNDROME

DEFINITION

Bartter syndrome is an autosomal recessive disease that causes a defect in chloride transport in the thick loop of Henle.



- Normally, the thick ascending loop of Henle provides urinary concentration mechanisms, it reabsorbs up to 30% of filtered sodium via Na- K- 2Cl co-transport.
- Thick ascending loop also contributes to calcium and magnesium homeostasis by paracellular mechanisms via the electrochemical gradient created sodium chloride transport.
- The defect in transport affects chloride reabsorption, leading to loss of Cl, Na and K in urine.
- Failure to reabsorb Na leads to natriuresis and volume depletion, activating the Renal-angiotensin-aldosterone system (RAAS), thus activating aldosterone which reabsorbs Na in exchange of K.
- Also decreased paracellular reabsorption of calcium leads to hypercalciuria and hypocalcemia, magnesium usually unaffected.
- This whole mechanism leads to hypochloremic hypokalemic metabolic alkalosis.

PRESENTATION

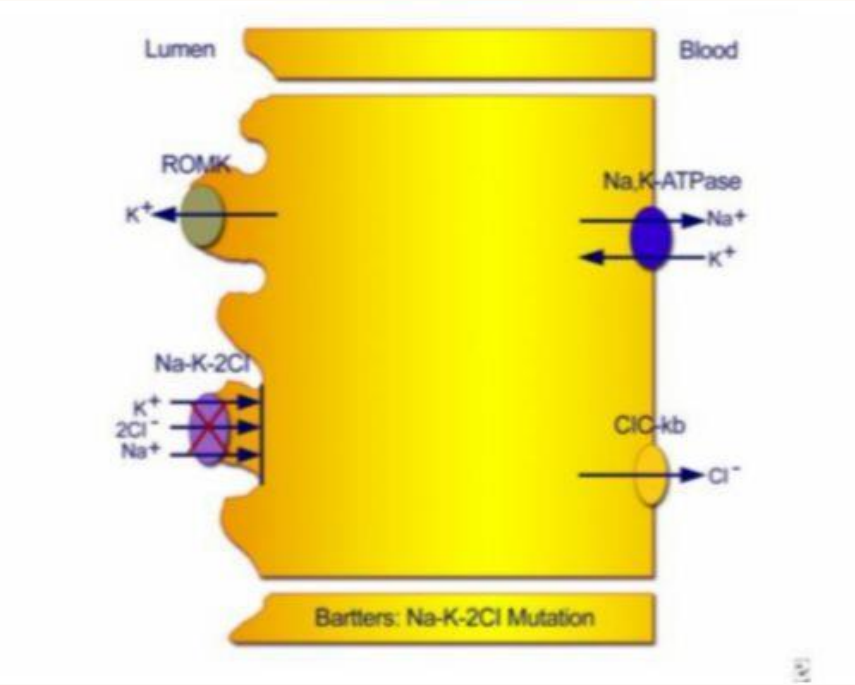
Bartter syndrome generally presents in early infancy, it presents as:

1. Persistent Polyuria, polydipsia and dehydration.
2. Electrolytes imbalance.
3. Failure to Thrive.
4. May progress to renal failure.
5. Symptoms of renal colic as a result of calcium stones.
6. May present antenatally with polyhydramnios.
7. Chronic hypokalemia may cause rhabdomyolysis and cardiac arrythmias.
8. Dysmorphic features: triangular face, large eyes with strabismus drooping mouth and protruding ears.

CLASSIFICATION

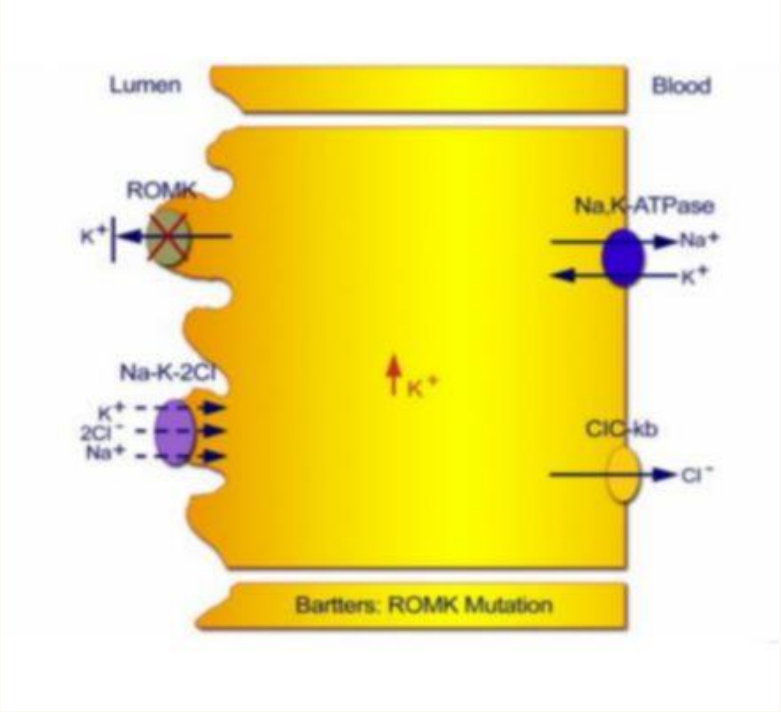
Bartter syndrome is classified into types I-V based on underlying genetic diagnosis:

- Type 1 Bartter: Mutation in sodium chloride/potassium co-transport gene results in defective reabsorption.



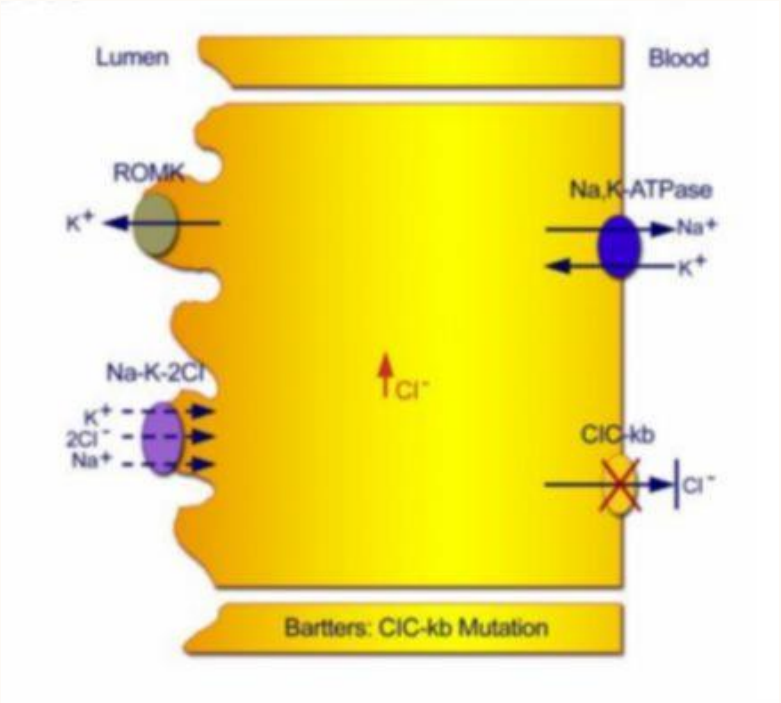
CLASSIFICATION

- Type 2 Bartter: Mutation in ROMK gene, resulting in an inability to recycle potassium from the cell back into tubular lumen, which inhibits Na, K, 2Cl co-transport.



CLASSIFICATION

- Type 3 (classic type): Mutation in CIC-kb chloride channel leading to inability of chloride to exit the cell with resultant inhibition of Na, K, 2Cl co-transport.



CLASSIFICATION

- Type 4: Defect in both CIC-ka and CIC-kb, presents antenatally with congenital hearing problems, this type is less prone to develop nephrocalcinosis but more susceptible to develop renal dysfunction.

- Type 5: Presents antenatally and is transient, resolving within the first 3 months of life.

DIAGNOSIS

Diagnosis is made by clinical features and laboratory findings:

- Laboratory Diagnosis:
  - ❖ Biochemical profile:
    - ❑ Metabolic alkalosis.
    - ❑ Hypokalemia.
    - ❑ Hypercalciuria.
    - ❑ Normal magnesium.
  - ❖ Venous Blood Gases
  - ❖ Renin/ aldosterone.

Confirmed by genetic testing.

DIFFERENTIAL DIAGNOSIS

Several conditions should be considered in infants with persistent hypochloremic metabolic alkalosis:

1. Insufficient chloride intake.
2. Cystic fibrosis.
3. Pyloric stenosis.
4. Congenital chloride diarrhea.
5. Bartter syndrome: Normal magnesium and hypercalciuria.
6. Gitelman Syndrome: Hypomagnesemia and low urine calcium.
7. Mineralocorticosteroid excess (hyperaldosteronism): Causes hypertension.
8. Thiazide diuretics.

MANAGEMENT

- Preventing dehydration.
- Maintaining nutritional status.
- Correction of fluid and electrolyte imbalance (correcting hypokalemia by high dose potassium supplementation).
- Infants and young children may require sodium supplements as well.
- Indomethacin (prostaglandin inhibitor): Since prostaglandin activates RAAS.
- Potassium sparing diuretics: Spironolactone.

CASE EXAMPLE

- An 8-week-old female infant presented to the emergency department with a 5-day history of intermittent non-bilious vomiting.
- It was progressively becoming more forceful in nature.
- She had associated hypoactivity.
- There was no associated fever, diarrhea or rashes.
- She was born at 3.7kgs, term at 38 weeks, to a healthy 38-year-old mother (G3P2).
- The pregnancy was unremarkable apart from some mild polyhydramnios noted on an ultrasound during an antenatal visit.
- There was no significant medical, family, social or developmental history.

- On physical examination, the patient was noted to be moderately dehydrated. Following fluid resuscitation (20ml/kg) with normal saline, the patient became more alert.
- Her vitals were normal for her age; her blood pressure was 80/65mmHg and her heart rate was 140bpm, the patient weight was 3.85 kg (5th percentile).
- The patient’s head, neck, respiratory and cardiovascular examinations were unremarkable.
- Her abdomen was soft and mildly distended, with no palpable masses or hepatomegaly.
- The patient had no dysmorphic features.

LABS

Initial investigations shows:

- **Serum Potassium: 2mmol/L [N3.5-5.5].**
- **Serum Sodium: 131mmol/L [N135-145].**
- **Serum Chloride: 57mmol/L [N95-105].**
- **Serum Bicarbonate: 51mmol/L [N22-32].**

Further investigations shows:

- Glucose: 7.1mmol/L.
- **Blood Urea Nitrogen: 1.4mmol/L [N2.1-8.5].**
- **Plasma Renin: 126.6ng/L/s [N0.13-0.9].**
- **Plasma Aldosterone: 2900pmol/L [N<444].**
- **Creatinine: 26.5 µmol/L [N53-97.2].**
- **VBG values showed a pH of 7.59, pCO2 of 52mmHg, pO2 of 50mmHg and HCO3 of 50mmol/L.**
- Calcium and magnesium levels were normal.
- Abdominal ultrasound was normal (no evidence of hypertrophic pyloric stenosis).

This patient was rehydrated and stabilized, then she was maintained on oral potassium and sodium supplementation as well as indomethacin and spironolactone.

Several outpatient visits at pediatrics and nephrology clinics shows a well-hydrated and thriving infant with no evidence of nephrocalcinosis on serial ultrasound

HYPOKALEMIC METABOLIC ALKALOSIS WITH HYPERTENSION

LIDDLE SYNDROME

- Liddle syndrome is an autosomal dominant disorder caused by a gain of function mutation SCNN1A/ B which leads to an upregulation of the distal sodium channels.
- These channels are usually upregulated by RAAS, but in this case it acts independently.
- This leads to excessive sodium retention and excessive hydrogen and potassium loss.
- So, the patient will present with hypertension, hypernatremia, hypokalemia, metabolic alkalosis and low renin/ aldosterone levels.
- It is usually diagnosed in early childhood as severe resistant hypertension, but some cases aren’t diagnosed until adulthood.

It is managed by:

- Low sodium diet.
- Potassium supplementation.
- Sodium channel blocker as amiloride.

THANK YOU