Original Article

Demystifying renal tubular disorders in children: A simplified approach

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ABSTRACT

Renal tubular disorders essentially include all disorders of the highly specialized channels of the renal tubular system, from the proximal convoluted tubule to the cortical and medullary collecting ducts. This tubular system is responsible for reabsorption of 99% of glomerular ultrafiltrate, which contains a large amount of fluid (approximately 180 L/day) as well as most electrolytes and many metabolites such as glucose (G), amino acids, bicarbonate (HCO^{3-}), phosphate (PO_4^{3-}), and low-molecular-weight proteins and is essential for maintaining fluid, electrolyte, and acid–base balance. In this review, we will briefly discuss when to suspect a renal tubular disorder, a simplified algorithm for evaluation, and specific mutations of a few common disorders.

Key words: Bartter syndrome, Diabetes insipidus, Renal tubular acidosis

Renal tubular disorders include all disorders or defects in the highly specialized channels present throughout the renal tubular system, beginning from the proximal convoluted tubule (PT) to the thick ascending loop of Henle (TAL), the distal convoluted tubule (DCT), the connecting tubule, and the cortical and medullary collecting ducts (CD). This tubular system is responsible for the reabsorption of 99% of the glomerular ultrafiltrate, which contains a large amount of fluid (approximately 180 L/day), along with most of the electrolytes and many metabolites such as glucose (G), amino acids, bicarbonate (HCO_3^-), phosphate (PO_4^{3-}), and low-molecular-weight proteins (LMWP) (Fig. 1) [1]. This is vital for maintaining the normal milieu in the human body, and any disorder affecting it can lead to life-threatening fluid, electrolyte, and acid–base imbalances.

In a nutshell, tubular functions include [2-5]: major solute and electrolyte absorption, mainly in PT and in smaller amounts throughout the renal tubule, including the distal tubules and CD; acid–base balance through bicarbonate reabsorption in PT; proton secretion (H+) in the DCT and CD; and concentration of tubular fluid by water absorption primarily in the DCT and CD.

Dehydration, high or normal to low blood pressure, dyselectrolytemia, metabolic acidosis or alkalosis, and other specific features are common in children with primary renal tubulopathies. Thus, tubular disorders should be suspected in children with one or more of the following clinical features: [2-5] – antenatal polyhydroamnios unaccounted for by anatomical lesions, failure to thrive, growth retardation, polyuria and polydipsia, preference for salty or savory foods, recurrent vomiting, unexplained intermittent dyspnea, refractory rickets, history of recurrent admissions for dehydration or infections, hearing loss or visual symptoms, and family history of unexplained deaths.

It is also important to remember that tubular disorders are very rare, and more common conditions such as diabetes mellitus and chronic kidney disease should always be ruled out first. Furthermore, children should not be evaluated for tubular disorders in the presence of an intercurrent or acute illness that can potentially influence fluid-electrolyte and acid–base balance. Once the diagnosis is suspected, it is very important that we evaluate these children systematically so as to not miss the diagnosis and ensure appropriate treatment in a timely manner.

First, we must confirm the presence of polyuria and evaluate its cause. Polyuria is defined as the passage of an excessive volume of urine (>2000 ml/m^2/day or >4 ml/kg/day) [6]. A simple algorithm (Fig. 2) to approach a child with or without polyuria and a suspected renal tubular disorder is given below in Fig. 1 [2-4,7,8]:

Table 1 gives details of the tests mentioned in the algorithm above and their normal values.

A summary of the most common tubular syndromes affecting various parts of the tubule, as well as the most frequently affected transporters and underlying mutations, is provided below:

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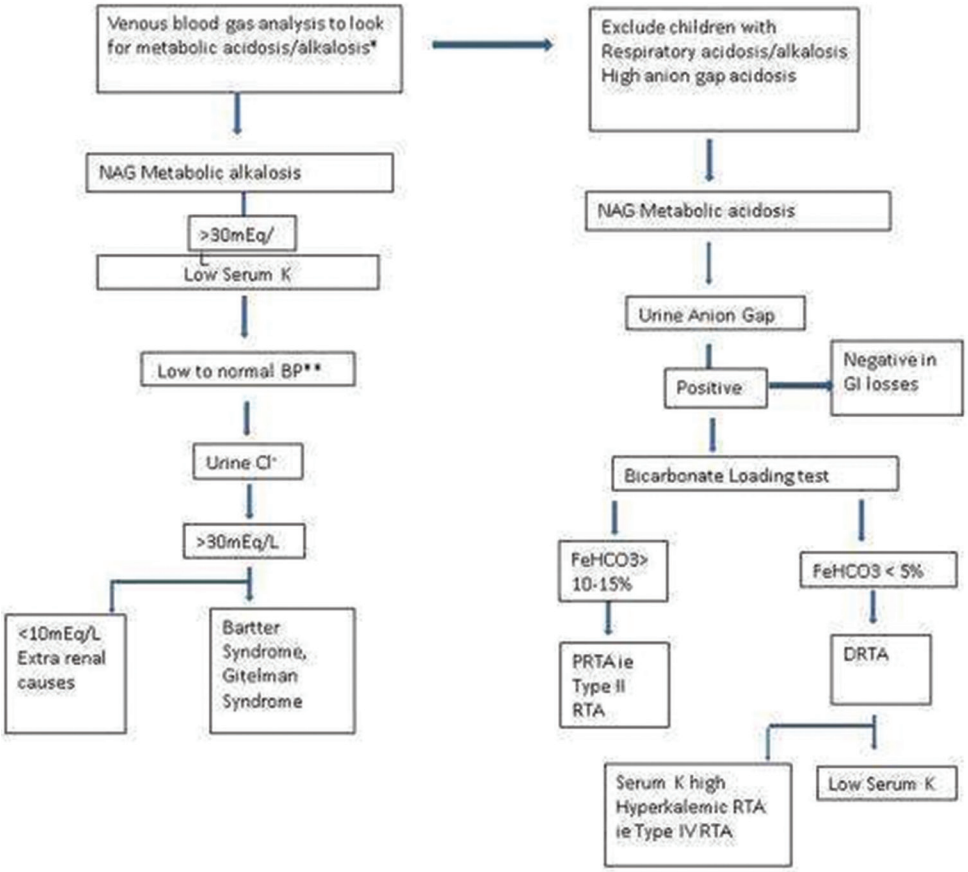

Figure 1: Algorithm to approach a child with or without polyuria with suspected renal tubular disorder

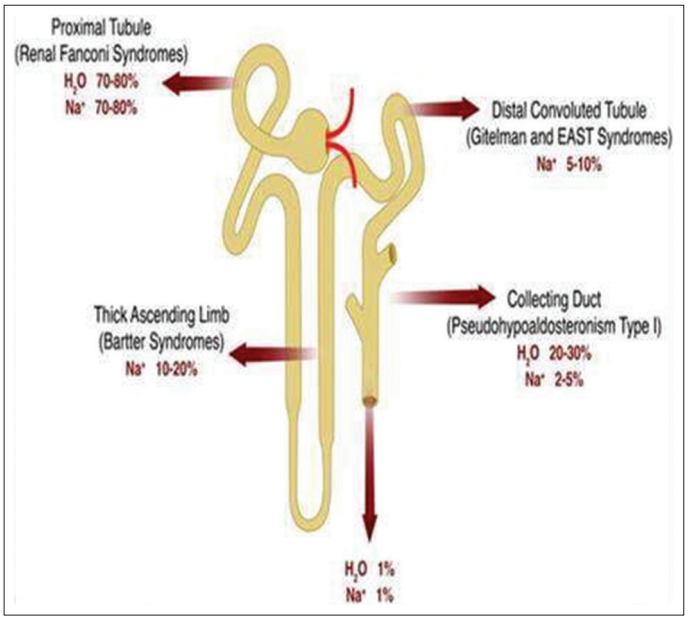

Figure 2: Various segments of the tubules and the absorption of sodium, other electrolytes, and water in these segments

Proximal Tubule Acidosis and Renal Fanconi Syndrome (RFS)

The acid–base balance is maintained by the sodium-hydrogen exchanger (NHE3), which secretes H+ in exchange for Na (Fig. 3). In the presence of luminal Carbonic Anhydrase IV (CA IV), the filtered HCO_3^- combines with H+ to form H_2CO_3,

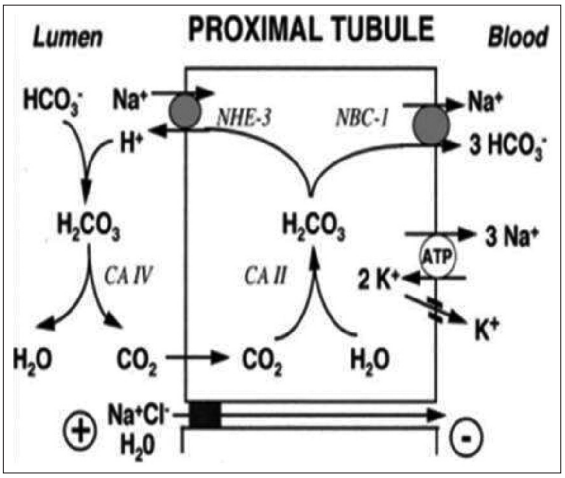

Figure 3: Reabsorbtion of sodium and bicarbonate in the PT

which is then converted into CO_2 and H_2O. This CO_2 diffuses inside the cell, and then HCO_3, formed by the action of CA II, gets absorbed through the sodium bicarbonate cotransporter (NBC1) at the basolateral membrane.

Ammoniagenesis also takes place in PT from glutamine. Therefore, mutations in NHE3 or NBC1 cause metabolic acidosis. The AR mutation in CA II causes metabolic acidosis as well as osteoporosis [9].

However, global dysfunction of PT is more common, and RFS is the name given to global proximal tubular function leading to phosphaturia, glucosuria, aminoaciduria, LMWP uria, and

Table 1: Common tests used to diagnose and further classify common tubular disorders [2,3,6,7]

S. No.	Test	Test methodology and interpretation
1	Plasma AG	$Na+ - (Cl- + HCO_3^-)$ anion gap The anion gap in normal plasma is 10-12 mEq/L Normal anion gap, that is, hyperchloremic metabolic acidosis, is seen in increased RTA or chronic diarrhea
2	UAG	Under normal conditions, urine Na+, K+, and Cl Normal UAG is positive Metabolic acidosis results in a negative UAG Positive UAG is seen in RTA
3	U-B CO2	A low U-B CO_2 (10 mm Hg) level indicates distal RTA U-B CO_2 levels >20 mm Hg are considered normal in the proximal RTA However, U-B CO_2 should be estimated only after serum bicarbonate levels have returned to normal, which can be accomplished with 2–4 mEq/kg of oral sodium bicarbonate dosing
4	Fractional excretion of bicarbonate	Calculated as Serum Creatinine 100- Urine HCO_3 Creatinine in urine – serum HCO_3 More than 15% indicates proximal RTA and less than 15% indicates distal RTA Fractional excretion of bicarbonate should be calculated Only after serum bicarbonate levels have returned to normal, as previously described
5	Fractional excretion of phosphate	PO_4^{3-} excretion fraction (%) = PO_4^{3-}x plasma creatinine 100 urine Plasma PO_4^{3-} urinary creatinine PO_4^{3-} tubular reabsorption (%) = 100 - PO_4^{3-} fractional excretion Tubular maximum for PO_4^{3-}corrected for GFR (TmP/GFR) estimated using the normal 2.8–4.4 mg/dL is a better index of renal threshold for PO_4^{3-}
6	Ammonium chloride test or furosemide-fludrocortisone test (FF test)	The ammonium chloride test has been used for the diagnosis of dRTA, but it causes gastric irritation, nausea, and vomiting in a large majority of patients and is, therefore, largely replaced by the FF test. Furosemide administration increases the delivery of sodium ions to the distal tubule. With an intact distal tubular acidification mechanism, these sodium ions get reabsorbed in exchange for H+ions, resulting in acidic urine. The avidity of this effect is greater in a sodium-depleted state or following fludrocortisone administration. Procedure: 1. Determine early morning urine pH following overnight fasting 2. Check baseline VBG and Na, K. If K is below 3.5, provide supplements 3. Administer furosemide 1–2 mg/kg (maximum 40 mg) and fludrocortisone 0.025 mg/kg (maximum 1 mg) orally. *Ad libitum* fluid intake is allowed 4. Using a pH meter, determine urine pH every hour for the next 6 h, or until urine pH reaches 5.3 5. Run a simultaneous control 6. If the baseline pH is 5.3, the test is not required Results: Urine pH 5.3 rules out a distal acidification defect
7	WDT	Suspected patients are not allowed to drink any fluids until they have lost 3% of their body weight or have three consecutive hourly urine osmolality values that are within 10% of each other, which usually takes 6–8 h. Urine osmolality >750 mOsm/kg is seen in primary polydipsia. Patients with Osmolality 750 mOsm/kg after WDT are given vasopressin intranasally (10–20 g) or subcutaneously (1–3 g), and urine osmolality is measured after 1–2 h. Increase in urine osmolality by >50% of baseline, 1 h after vasopressin administration, is diagnostic of central diabetes insipidus; in nephrogenic diabetes insipidus, there is no or a minimal increase in urine osmolality

UAG: Urine anion gap, WDT: Water deprivation test, AG: Anion gap

metabolic acidosis. It can be primary due to a mutation in Na+-K+ ATPase, resulting in fanconi renal tubular syndrome with variable phenotype, or secondary to systemic inherited causes such as galactosemia, Wilson's disease, cystinosis, mitochondrial cytopathies, and various drugs, including nucleotide reverse transcriptase inhibitors such as tenofovir and adefovir and anticancer drugs like ifosfamide. Besides transporters for acid–base balance, PT also has sodium-phosphate cotransporters (NaPi-IIa and NaPi-IIc) on the luminal side; an AR mutation in NaPi-IIa causes infantile hypercalciuria with nephrolithiasis, whereas a mutation in NaPi-IIc leads to hypophosphatemic rickets with hypercalciuria and nephrocalcinosis (Table 2). In these cases, hypercalcemia with hypercalciuria is caused by suppressed FGF-23 due to low PO_4^{3-} levels, which increases 1a-hydroxylase activity.

Bartter Syndrome with Pathology in the TAL, Gitelman Syndrome (GS) with Similar Biochemical Features but due to Mutations Affecting the DCT, and Related Disorders

The furosemide-sensitive Na+-2Cl2-K+ cotransporter (NKCC2) is the main apical sodium transporter in the TAL (Fig. 4).

Table 2: Summary of common mutations and their affected channels [3,6,8,9,15-18,20-22]

Renal disorder	Common mutations	Mode of inheritance	Associated features
DRTA	ATP6V0A4 ATP6V1B1 FOXI1 WDR72 SLC4A1	AR AR AR AR AD/AR	SNHL (early onset) SNHL (variable onset) SNHL (early onset) Amelogenesis imperfecta, type IIA3 Hemolytic Anemia (Southeast Asian Ovalocytosis/Spherocytosis) milder form of DRTA
Primary Fanconi syndrome	SLC34A1 mutation in NaPi-II cotransporter EHHADH gene mutation HNF4A gene (R76W) mutation	AR AD AD	Neonatal hyperinsulinism and macrosomia.
Isolated Proximal RTA	Mutation in the kidney isoform of NBCe1mutation: SLC4A4 mutation	AR/AD (rare)	Bilateral glaucoma, cataracts and band keratopathy. Intellectual impairment, elevated serum amylase levels without pancreatitis
Type III RTA	Deficiency of CA II	AR	Osteopetrosis and cerebral calcification
Hypophosphatemic rickets with hypercalciuria (HHRH)	NaPi-IIc	AR	Hypophosphatemic rickets hypercalciuria, and nephrocalcinosis
BS I	SLC12A1 encoding NKCC2	AR	Antenatal Bartter syndrome
BSII	KCNJ1encoding Renal outer medullary potassium (ROMK) channel	AR	Antenatal Bartter syndrome with transient hyperkalemia
BSIII	CLC-Kb	AR	
BSIV A	BSND	AR	Antenatal Bartter syndrome and sensorineural deafness
BSIV B	Barttin (B-subunit of CLC-Ka and CLC-Kb)	AR	
BS V	MAGED-2(melanoma associated antigen D-2)	XR	Transient antenatal BS, severe polyhydramnios, postnatal polyuria, and metabolic alkalosis resolves in few months
Gitelman Syndrome	SLC12A3 encoding NCC		Usually late presentation, hypomagnesemia
EAST/SeSAME syndrome	KCNJ10 encoding for Kir 4.1(potassium inward rectifying channel in DCT)	AR	Epilepsy, ataxia, sensorineural deafness, and tubulopathy
PHA I (AR)	ENaC subunit α,β and γ	AR	Hyponatremia, hyperkalemia, acidosis, and lung disease
PHA I (AD)	MR	AD	Transient neonatal salt wasting, hyponatremia, hyperkalemia, and acidosis
Nephrogenic Diabetes Insipidus	AVPR2 AQP2	X-linked AR/AD	

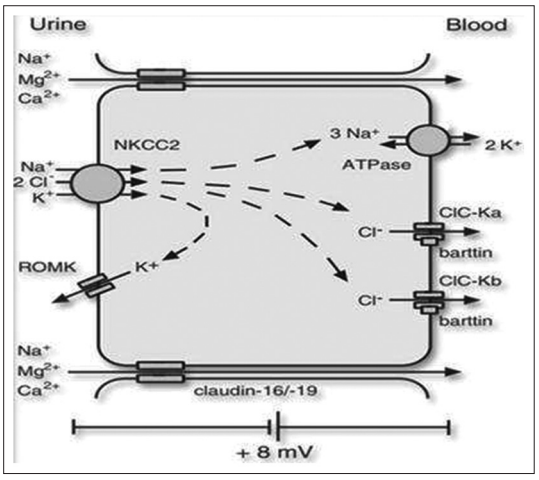

Figure 4: Various channels in TAL

Mutations in this gene cause Bartter Syndrome type 1 (BS1). Another apical potassium channel, Renal Outer Medullary (ROMK), is important for the functioning of NKCC2, and mutations in this channel cause BS type 2. Mutations in NKCC2, ROMK, and BSND cause severe antenatal forms of BS.

The basolateral exit of chloride ions (Cl) takes place through the chloride channels ClC-Ka and ClC-Kb. A mutation in ClC-Kb leads to BS type 3, and a mutation in the barttin protein (BSND) (the subunit for ClC-Ka and ClC-Kb) results in BS type 4.

The positive transepithelial potential of the lumen drives the paracellular absorption of cations such as Ca++ and Mg++ through paracellular channels claudins 16 (CLDN16) and 19 (CLDN19) (Fig. 4). Thus, the paracellular transport of divalent cations (Ca and Mg) in TAL is linked to sodium transport. Mutations in these channel proteins cause familial hypomagnesemia with hypercalciuria and nephrocalcinosis with or without sensorineural deafness [10].

The NCCT channel at the DCT is mainly responsible for salt absorption through the sodium chloride cotransporter

(NCCT) (Fig. 4). Active or transcellular absorption of Ca++ and Mg++ occurs through TRPV5 and TRPM6 channels on the apical membrane, and chloride transport occurs through the basolateral ClCKb channel. A mutation in the NCCT channel at the DCT causes GS. GS is characterized by the combination of hypokalemic and hypochloremic alkalosis with hypomagnesemia and hypocalciuria. Most patients are adolescents or adults and are discovered when evaluated for cramps, dizziness, aches, and fatigue [3,10-12].

Distal Renal Tubular Acidosis (DRTA) or type 1 RTA with pathology in the DT

Acid–base balance in distal tubules is mainly concerned with proton (H+) secretion occurring through H-ATPase and H-K ATPAse pumps in alpha-intercalated cells (Fig. 5). A very minute amount of H+ is secreted in free form, leading to low urinary pH, which cannot go below 4.5–5. A fixed amount of acid is secreted as titrable acid (mainly H_2PO_4). The major part of acid is secreted as NH4+, especially in conditions with extrarenal metabolic acidosis. Cytosolic CA II causes the production of H_2CO_3 from H_2O and CO_2, which, then, ionizes into HCO_3 and H+. HCO_3^- ion is absorbed in the blood through the basolateral channel anion exchanger (AE1) [13].

Net acid excretion (NAE) = titratable acid (H_2PO_4) + ammonium ($NH4^+$)-urinary (HCO_3^-) [14]

The primary pathology in DRTA or type 1 RTA is the impaired ability of the alpha-intercalated cells to secrete protons, causing normal anion gap metabolic acidosis. Hypokalemia is usually present and is attributed to the impaired potassium and proton secretion in the CD in exchange for sodium reabsorption. The excess acid in the blood is mainly buffered by the bones, which, together with impaired tubular calcium reabsorption in the presence of acidosis, results in hypercalciuria, which leads to nephrocalcinosis and/or nephrolithiasis in the long run [2,7,14].

The causative mutations of dRTA are chiefly: both autosomal dominant and recessive mutations in SLC4A1, which encodes the anion exchanger AE1, and recessive mutations in ATP6V0A4 and ATP6V1B1, expressed on the apical side of the intercalated cells as well as in the inner ear. Mutations in FOXI1, which encodes a transcription factor important for acid-secreting epithelia, and WDR72, which is hypothesized to be involved in intracellular trafficking, are also implicated in the causation of dRTA [15-19].

The CD is the tubule's final segment, which includes the epithelial sodium channel (ENaC), which, despite absorbing only a small amount of sodium, is critical. A loss of function mutation in ENaC causes AR type pseudohypoaldosteronism type I (PHA I), which manifests as severe salt-losing tubulopathy, skin rash, and lung involvement in the early infancy. However, AD type PHA I, which is caused by a mutation in the mineralocorticoid receptor, only manifests in the kidney.

Table 2 gives a summary of the presenting features, channels involved, and most common mutations of the tubulopathies discussed above.

Another disorder that presents with predominantly polyuria and resultant frequent episodes of dehydration and affects mainly the CD is nephrogenic diabetes insipidus (NDI).

NDI

Besides solute absorption and maintenance of acid–base balance, the final concentration of urine takes place in CD cells by pure water absorption through aquaporin-2 channels (AQ-2) in the luminal membrane of the CD cell. In conditions of volume depletion or increased serum osmolality, increased release of the hormone arginine vasopressin (AVP) occurs from the posterior pituitary, which, then, binds with the specific V2 receptor (AVPR2) on the basolateral side. The V2 receptor is a G-protein coupled receptor that activates

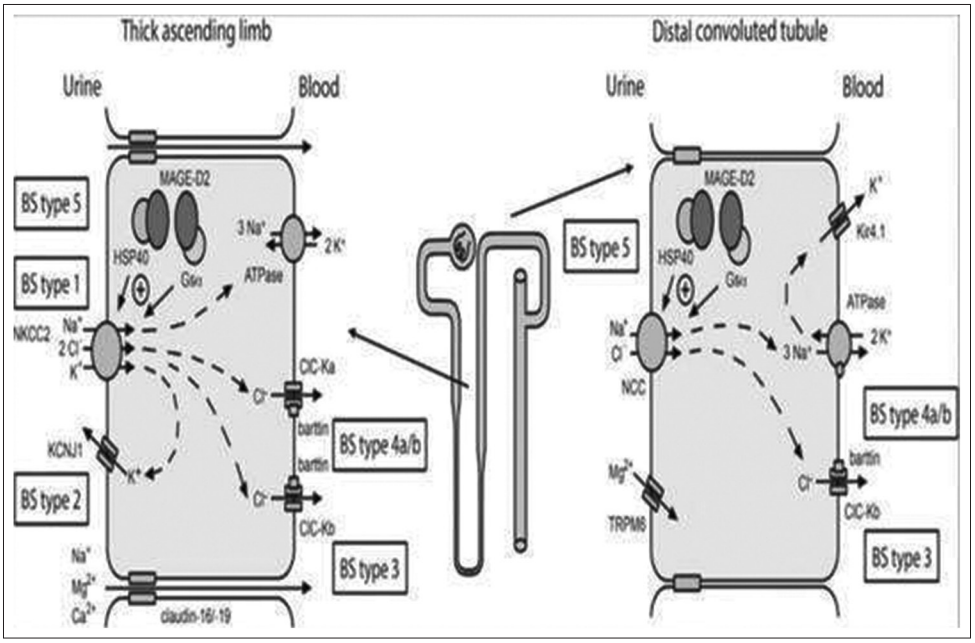

Figure 5: Various channels in TAL and DCT and associated mutations

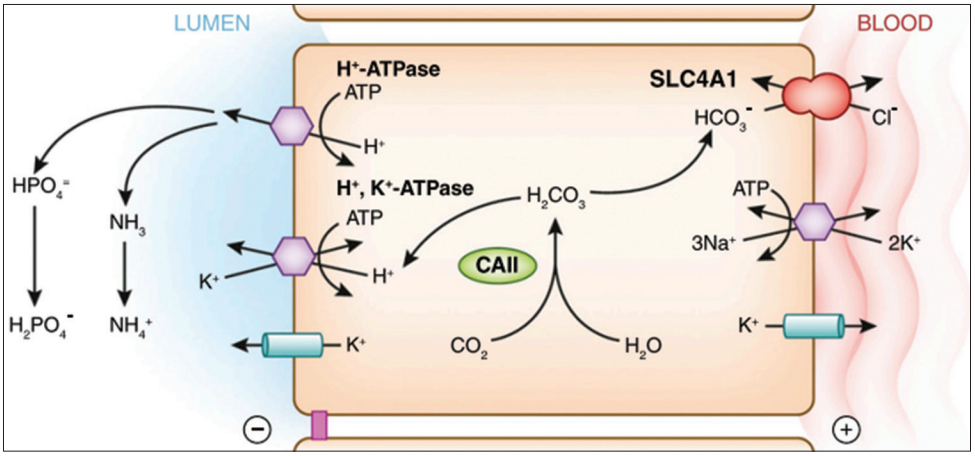

Figure 5: Various channels in α intercalated cell of DCT

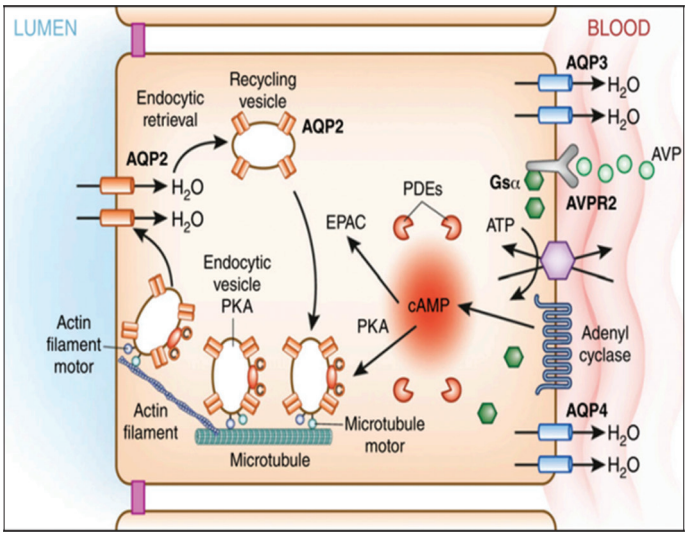

Figure 6: Water absorption through aquaporin-2 channels (AQ-2) in the CD

cAMP through adenylyl cyclase. Through PKA, there is increased phosphorylation of AQ2 channel proteins, which are present in monomer form in endocytic vesicles. When AQ2 is phosphorylated and activated, it forms a homotetramer that is trafficked to the luminal side and incorporated into the luminal membrane (Fig. 6).

Primary NDI is associated with mutations in two genes, AVPR2 (X-linked) and AQP2 (AR), the former being responsible for about 90% of cases. Primary inherited NDI presents in the early weeks of life with recurrent fever, feed intolerance, irritability, dehydration, polyuria, and failure to thrive, but polyhydroamnios is usually not seen [6].

CONCLUSIONS

RTAs are a wide spectrum of disorders that present with variable symptoms and severity among children. A protocolized and stepwise approach helps to identify the disorder and initiate appropriate therapy, which will ensure that these affected children grow well.

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