

Renal Tubular Acidosis in Childhood

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Abstract: A patient in pediatric who presented with hyperchloremic metabolic acidosis, after ruling out gastrointestinal origin should look for renal tubular acidosis (RTA). This usually inherited protein defect of tubules that are needed in acid-base regulation. "According to pathophysiology, there are four types. Distal type 1 RTA, proximal type 2 RTA, mixed-type 3 RTA, and type 4 RTA based on family history. The pattern of genetic inheritance follows autosomal recessive and autosomal dominant. In western countries, the autosomal dominant form is the most common, while autosomal recessive is mostly in the eastern especially Arab nation due to consanguineous marriage. However, in the literature, there were some cases reported as a secondary form in children that mostly associated with autoimmune diseases but not exclusively as in glucose-galactose malabsorption. A defect of reabsorption, secretion or generations of some ions, are the main mechanism of RTA. The patient may present with various types of symptoms like recurrent stone formation, muscles weakness, failure to thrive, and dehydration and most prominent is hypokalemia, but hyperkalemia may present too as in type 4. There are some extrarenal symptoms associated with RTA like, early or late deafness, hemolytic anemia, ocular problems (cataract glaucoma), neurological (mental retardation), osteopetrosis and many others. The diagnostic approaches of RTA patient are the clinical manifestation in which the suspected patients undergo laboratory investigation and genetic analysis too. RTA treatments are depending on nature of the disease is it primary or secondary form. Primary manage with drugs usually according to the type and may need other intervention to manage the consequences. The secondary form is managed by treating the underlying disease.

Keywords: gastrointestinal origin, renal tubular acidosis (RTA).

I. INTRODUCTION

RTA is a group of chronic diseases that results from a failure of renal tubules reabsorption of bicarbonate or to secrete hydrogen ions. The adult form of the disease is almost diagnosed as secondary to drugs, toxins or systemic diseases, while in pediatric is as a result of a genetic defect in protein needed in bicarbonate reabsorption and regeneration, and hydrogen ions secretion.

"According to pathophysiological basis four types of RTA are distinguished: type 1 is caused by the inability of distal convoluted tubules and collecting tubules to maximally increase the urinary elimination of hydrogen ions in the presence of metabolic acidosis; type 2 RTA result from impaired bicarbonate ions reabsorption in proximal tubules; type 3 RTA is mixed of type 1 and 2; type 4 RTA is caused mainly by defective production of ammonium resulting from either aldosterone deficiency or aldosterone resistance" (Rodríguez-Soriano, 2000).

Physiology of renal Acidification:

Acid base balance depends mainly on two processes (1) reabsorption of bicarbonate which mainly takes place in proximal convoluted tubules, and (2) elimination of acids through the urinary buffer, and secretion of ammonium which fundamentally occurs in distal convoluted tubules and collecting ducts (Rodríguez-Soriano, 2000).

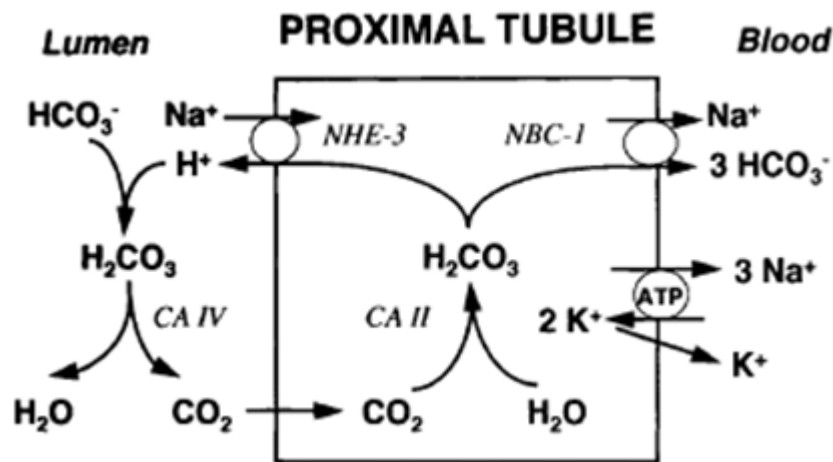
Bicarbonate reabsorption:

Most processes occurring here are "hydrogen secretion at luminal membrane via NHE3, (Na-H exchanger) and bicarbonate in the basolateral membrane through Na^+ - HCO_3^- cotransporter.

In the proximal tubules, carbonic acid (H_2CO_3) is made inside the cell by the condensation of water and CO_2 , this reaction catalyzed by carbonic anhydrase enzyme (CAII). The HCO_3^- and the H^+ is secreted in the basolateral side with Na^+ cotransporter (passively) and exchange in luminal side respectively. The secreted hydrogen ions react with filtered Bicarbonate ions to produce luminal carbonic acid, which rapidly disassociates into CO_2 and water by the luminal carbonic anhydrase (CA IV). Luminal CO_2 is able freely to penetrate the cell membrane to the cytoplasm to complete the reabsorption cycle. Metabolic acidosis can stimulate carbonic anhydrase enzymes (CA).

A second main task of the proximal tubules is ammonia (NH_3) formation from glutamine; the rate-limiting enzymes of this reaction are glutaminase and phosphoenolpyruvate carboxylase. Both enzymes are up regulated by chronic acidosis.

The influence of Proximal HCO_3^- reabsorption are “luminal HCO_3^- concentration and flow rate, extracellular fluid volume, peritubular HCO_3^- concentration and PCO_2 , Cl^- , K^+ , Ca^{2+} , phosphate, parathyroid hormone, glucocorticoids, α -adrenergic tone, and angiotensin II” (Rodríguez-Soriano, 2000).



“Fig. 1 Schematic model of bicarbonate (HCO_3^-) reabsorption in proximal convoluted tubule. The processes occurring are H^+ secretion at the luminal membrane via a specific $\text{Na}^+\text{-H}^+$ exchanger (NHE-3) and HCO_3^- transport at the basolateral membrane via a $1\text{ Na}^+\text{-}3\text{ HCO}_3^-$ cotransporter (NBC-1). Cytoplasmic carbonic anhydrase II (CA II) and membrane-bound carbonic anhydrase IV (CA IV) are necessary to reabsorb HCO_3^- ” (Rodríguez-Soriano, 2000).

Distal urinary acidification:

Urinary acidification in the distal nephron happened by three associated processes: (1) reformation of the minor portion of filtered HCO_3^- that seeps reabsorption proximally (10%–20%); (2) “titration of divalent basic phosphate (HPO_4^{2-}), which is converted to the monovalent acid form (H_2PO_4^-)”; and (3) intraluminally build up of NH_3 , which is buffers of hydrogen ion to produce non-diffusible ammonium (NH_4^+).

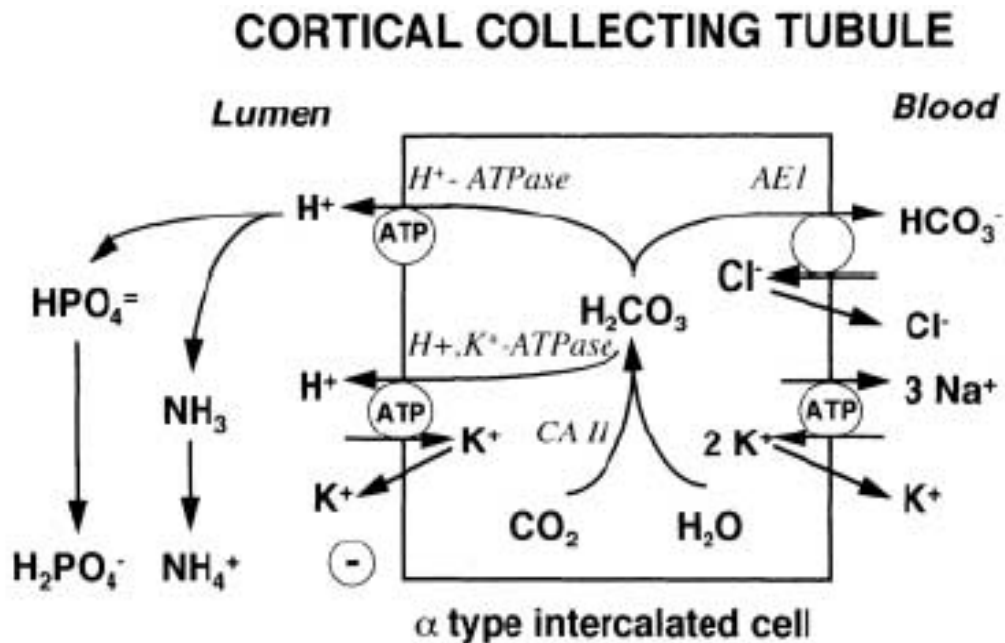
The thick ascending limb of loop of Henle reabsorbs about 15% of the filtered HCO_3^- by a mechanism like to that in the proximal tubules.

NH_4^+ Absorption in the loop of Henle apical membrane occurs by a replacement for K^+ both in the $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$ cotransport system and in the $\text{K}^+\text{-H}^+$ antiport system. NH_3 can't diffuse back or only little amount due to the low permeability of medullary thick ascending limb. An NH_4^+ medullary concentration gradient is produced and intensified by countercurrent multiplication through NH_4^+ excretion into the proximal tubule and maybe into the thin descending limb of the loop of Henle. The driving force of diffusional entry of NH_3 into the collecting tubule increases as a result of build up of the medullary interstitium NH_3 , the high acidity of the tubules facilitate this action at this level. Reduced of diminished distal acidification of urine may result in any abnormalities in $\text{NH}_3/\text{NH}_4^+$ synthesis and transportation.

Acidification of urinary system occurs mostly in the distal collecting tubules. In the cortical collecting tubule, the intercalated cells are involved in both hydrogen and bicarbonate excretion, while the principal cells are in charge of Na^+ reabsorption and K^+ secretion. There are two kinds of intercalated cells, differ in their function and their structure. “The α -cell is responsible for hydrogen secretion, and the β -cell is responsible for bicarbonate secretion”.

The α -type-intercalated cell is the fundamental pump for luminal H^+ secretion, but it is also extremely affected by the luminal electronegativity produced by active Na^+ transport happening in the principal cells. The H^+/K^+ -ATPase is also contributed in H^+ secretion, but its physiological function is perhaps more connected to K^+ than to acid-base homeostasis. Intracellularly formed HCO_3^- withdraws from the cell by Cl^-/HCO_3^- exchange.

External medullary collecting tubule is a special segment, in which does not reabsorb Na^+ or secrete K^+ and only continues H^+ secretion (Rodríguez-Soriano, 2000).



“Fig.2 Schematic model of H^+ secretion in cortical collecting tubule. The main pump for luminal H^+ secretion in the α -type intercalated cell is a vacuolar H^+ -ATPase. A H^+/K^+ -ATPase is also involved in H^+ secretion. Intracellularly formed HCO_3^- leaves the cell via Cl^-/HCO_3^- exchange. Cytoplasmic CA II is necessary to secrete H^+ ” (Rodríguez-Soriano, 2000).

The lumen of medullary collecting tubule is positive, and H^+ need to be secreted against the electrochemical gradient, the Na^+ -independent process controlled by the H^+ -ATPase. Aldosterone can affect H^+ secretion, but it is not inhibited of affected by agents that block Na^+ transporter. The terminal part, the inner medullary-collecting duct, also contributes to distal acidification. The H^+ secretion here is like the process explained in the α -intercalated cell, but its significance is to control renal H^+ secretion overall. All parts of the collecting tubule have so much of cytosolic carbonic anhydrase II, and luminal carbonic anhydrase IV that is bound to the membrane.

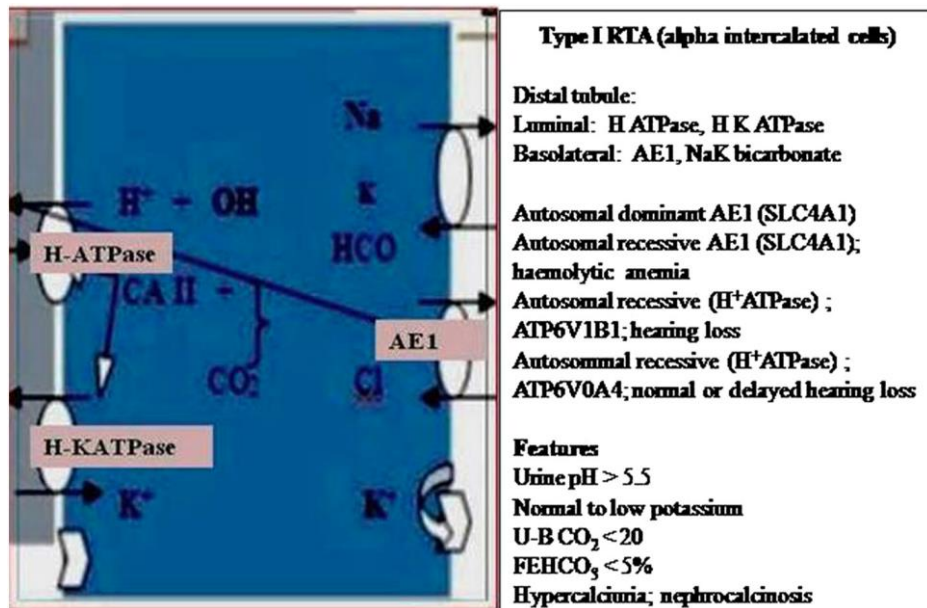
Anion exchangers (AE): Exchange of Cl^- and HCO_3^- at cell membranes. “There are three isoforms: AE1, AE2, and AE3. The red cell AE1 contributes to cytoskeletal structure and is essential for the respiratory function by interchanging Cl^- and HCO_3^- at red cell membranes”.

In the cortex and medulla of the kidney, the intercalated cells of collecting ducts exchanges anions at basolateral membranes of α type AE1. Also in the kidney AE2 is expressed, especially in the medullary thick ascending limb. AE3 is essentially expressed in myocardiocyte and brain (Rodríguez-Soriano, 2000).

II. RENAL TUBULAR DISEASES

Distal Renal Tubular Acidosis:

Also known as type 1, is a result of reduced capability to excrete H^+ by the α -intercalated cells in the collecting duct. Biochemically, this condition is typically had a hyperchloraemic metabolic acidosis with normal plasma anion gap, hypokalemia, and hypercalciuria with hypocitraturia leading to nephrocalcinosis. Notwithstanding an extreme metabolic acidosis, patients are incapable to acidify their urine, so they have urinary pH of higher than 5.5. Patients frequently come with puking, diarrhea/constipation, failure to thrive and/or rickets. Muscle weakness or paralysis can develop as a consequence of significant hypokalemia. (Besouw et al., 2017)



“Fig.3 Mechanism of distal RTA in the alpha intercalated Cell. Basolateral side chloride bicarbonate exchanger (AE1) excretes bicarbonate into the blood stream. Chloride homeostasis is maintained by the potassium-chloride cotransporter (KCC4) and the chloride channel (ClC-Kb)” (Sharma, Gupta, and Saxena, 2015)

When this activity fails and unable to balance the 1.5 mEq/kg body weight of nonvolatile acid produced every day as a result of the high protein intake by most people, which is manifest as RTA. A muscular paralysis is rare and infrequently described in children. Nephrocalcinosis and renal rickets can be a complication of distal RTA as consequence of calcium salts are constantly metabolized from bones for buffering. Paralytic attacks and nephrocalcinosis can be prevented, if prophylactic long-term bicarbonate therapy is given earlier than the age of four (Bresolin et al., 2005).

The clinical symptoms of hypokalemic paralysis as a result of RTA are similar to that of familial hypokalemic periodic paralysis, which is an uncommon genetic condition, with typically autosomal dominant inheritance. At the onset of the disease, usually in the middle to late childhood, periods of intense, intermittent muscle weakness is observed. This is frequently associated with high-carbohydrate low-potassium diet, infection, training, alcohol ingestion, or stress. Daily attacks might occur throughout early adulthood, but incidents decline in regularity in late adulthood, while the older patients may have a stable extremity weakness. A rapid drop in serum potassium concentration and in urinary retention of sodium, potassium, chloride, and water can trigger the attack. Glucose-insulin infusion may trigger an attack, and oral potassium salts temper the episode these can be diagnostic. Hypokalemia in familial hypokalemic periodic paralysis is not because of loss of potassium as it seen in distal RTA, but it is due to defects in its reallocation between intra- and extracellular compartments. Nowadays it is known the two mutations of Voltage-gated calcium or sodium channels on the skeletal muscles that cause the familial hypokalemic periodic paralysis (Bresolin et al., 2005).

Hypercalciuria is a consequence of high free serum calcium level that is from the bones, joint with the reduced expression of renal calcium transporters in metabolic acidosis. In turn can also cause nephrocalcinosis and, if remaining untreated, to renal stones formed. Nephrogenic diabetes insipidus is due to a reduced urinary concentrating ability, which presents as polyuria. Up to now, many genes are identified, as causes of distal RTA. Autosomal recessive inheritance is distinguished in mutations in genes that coding subunits of the vacuolar H⁺-ATPase. While another gene is inherited as autosomal dominant which encodes anion exchanger 1 (Besouw et al., 2017)

Hyperammonemia is usually caused by inborn error metabolism like a disorder of urea cycle, a defect of fatty acid oxidation or others like Reye Syndrome, lysinuric protein intolerance, and hepatic insufficiency, etc. But hyperammonemia as a consequence of distal renal tubular acidosis is extremely rare. This patient had gone through the usual genetic testing that causes hyperammonemia, but all parameters of metabolism were normal. No amino acid or ketones were detected in the urine. Therefore they ruled out metabolic disorders. Normal liver function test excludes liver disease. Infections also were excluded with normal WBC count and negative urine culture.

Eventually, a kidney ultrasonography, revealed medullary nephrocalcinosis, as part of the classic presentation of distal RTA. Although distal RTA is typically accompanied by a low rate of ammonia excretion in urine, this patient had

hyperammonemia. Ammonia (NH_3) is produced by cells of the proximal tubule, excreted into the tubular fluid, resorbed by the thick ascending limb of Henle. Build up in the medullary interstitium and eventually secreted in collecting ducts in the medulla. In response to metabolic acidosis, kidney increases the net excretion of acid, in which ammonia is the main component of it. By this, the chronic phase of metabolic acidosis and hypokalemia are stimulants of ammonia-gensis of the kidney, loop of Henle reabsorption of ammonia, and ammonia concentration of interstitium. The synthesis of NH_3 is increased from glutamine throughout chronic metabolic acidosis due to the raised activity of a sequence of crucial enzymes of ammonia-gensis (glutaminase, which deaminates glutamine, glutamate dehydrogenase, which converts glutamate to α -ketoglutarate, and α -ketoglutarate dehydrogenase, which then converts the α -ketoglutarate to glucose) over a reactions series that exhaust H^+ .

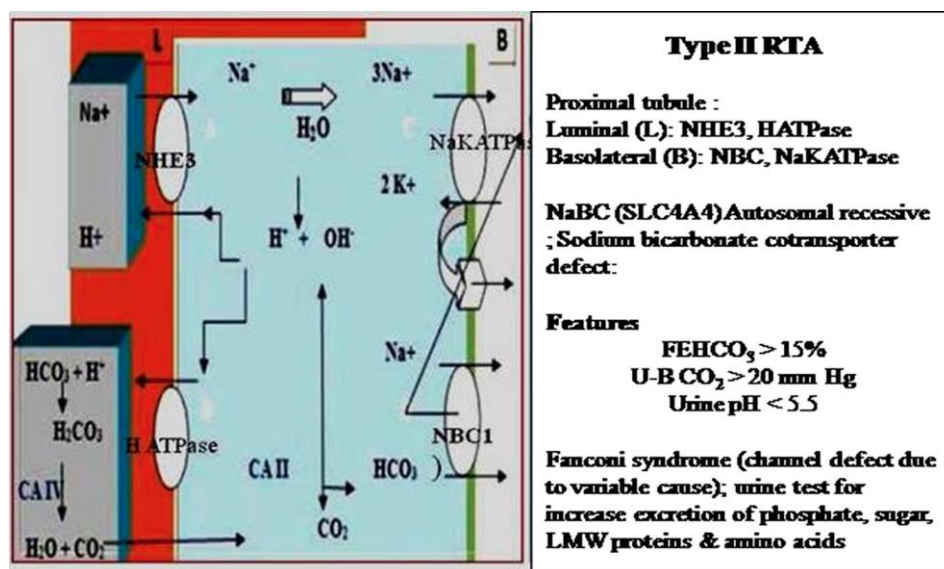
Furthermore, the rate-limiting enzyme is the cytosolic phospho-enolpyruvate carboxykinase, which converts α -ketoglutarate to glucose. In this patient hyperammonemia perhaps was due to the increased ammonia synthesis, in response to both metabolic acidosis and severe hypokalemia, in the existence of reduced ammonia excretion because of the distal RTA, as NH_4^+ in the urine, ammonia diffuses back into the interstitium of renal medulla and buildup of ammonia in the blood. Distal RTA was serious (pH of urine were higher than 7.0) and, thus, not so much of the ammonia synthesized newly (Seracini, Poggi, and Pela, 2005)

Incomplete dRTA (idRTA):

In comparison to the complete one, it does not reveal a metabolic acidosis in basal conditions. The clinical effects of idRTA are limited to recurrent nephrolithiasis and nephrocalcinosis. Recently it has been shown also skeletal effect, rickets in children and that 30% of adults with osteopenia and in 19% with osteoporosis had idRTA. Due to major skeletal growth in the pediatric age group, the clinical manifestations due to idRTA can be more severe in the childhood period (Sharma et al., 2007). The high pH of urine trigger loss of calcium to into urine. This loss consistently leads to release of calcium from the bone at a slower rate than in the typical RTA as a compensatory mechanism. This released of calcium is lost into the highly alkaline urine prolonging hypocalcemia, consequently a state of secondary hyperparathyroidism may develop. Parathyroid hormone act on renal tubules by increasing the excretion rate of bicarbonate and mineral salt into the urine (Oduwole, Giwa and Arogundade, 2010).

Proximal Renal Tubular Acidosis:

Also known as type 2 RTA. It is characterized by failure of proximal renewal of bicarbonate. This could be inherited or acquired, and can be isolated as a single defect or combined with other proximal tubular problems. The bicarbonate reabsorption mostly occurs as CO_2 following sodium dependent H^+ secretion thru Na^+/H^+ exchanger isoforms or via vacuolar H^+ -ATPase to a lesser extent, or other mechanisms, but also para-cellular transport of some bicarbonate may happen. The transport needs CA- 2 and 4.



“Fig.4 Mechanism of proximal tubular bicarbonate transport. sodium, potassium, bicarbonate ion, proton, hydroxyl ion, carbon dioxide, carbonic anhydrase, c sodium–potassium ATPase, d sodium bicarbonate symporter (NBC1), a sodium-proton exchanger (NHE3) and b Hydrogen ion ATPase excrete protons into the tubular lumen” (Sharma, Gupta, and Saxena, 2015)

Amongst inherited forms of RTA type 2, the autosomal dominant disorder is extremely rare with mostly unknown pathomechanism (dysfunction of the Na^+/H^+ exchanger has been suspected) 3. Autosomal recessive is more frequent form with ocular deformity, linked to kidney mutations in $\text{Na}^+/\text{HCO}_3^-$ cotransporter gene, which encodes the basolateral cotransporter. The activity of the cotransporter can cause membrane depolarization and to extracellular HCO_3^- accumulation. Newly potassium channel is identified, “named TASK2”, reuse K^+ and repolarizes the potential, defective function of this channel had been identified in mice with metabolic acidosis coupled with inadequate proximal reabsorption of bicarbonate. Previous studies have shown macromolecular interaction between CA-2 and $\text{Na}^+/\text{HCO}_3^-$ cotransporter not only at substrate level but also as protein-protein interaction.

Sporadic forms also reported, which are not categorized yet. Nevertheless, most cases of proximal RTA are not primary. Acetazolamide can block CA-4 by which can lead obviously to proximal RTA. The general proximal tubular syndrome can be caused by other genetic diseases (Fanconi’s; fructose intolerance, etc.), drugs and toxins (e.g. ifosfamide lead, mercury, and cadmium).

The presence of bicarbonaturia is typical of proximal RTA, with a higher than 15% of fractional bicarbonate excretion of when bicarbonate is given. Finally, urine acidification and acid–base balance is reached as plasma bicarbonate falls, it is sufficient for reabsorption to keep pace. Management may be challenging as administered base is frequently excreted before the wanted normalization is reached.

Defining loss of urinary bicarbonate will automatically diminish the body and lead in hyperchloraemic acidosis. The mutual retention of Cl^- and subsequent drop in strong ion deference will also describe the results.

It has been thought previously in acid-base balance, that the proximal bicarbonate reabsorption is controlled by pH. Recent studies of bicarbonate transport concluded that the experimental regulation would need both a CO_2 sensor and a HCO_3^- sensor. As pH sensor would not be adequate (Ring, Frische, and Nielsen, 2005).

Fanconi Syndrome:

It is a heterogeneous group of disorders of the proximal renal tubular cells that leads to loss of: low molecular-weight proteins, amino acids, glucose, bicarbonate, phosphate, uric acid, and cations, in the urine (Sanjad SA, 1997). Mostly, they correlate to multisystem disorders. Generally, we can categorize the mechanism of these disorders: “as either (i) accumulation of a toxic metabolite (e.g. cystinosis, tyrosinaemia, galactosaemia, Fanconi–Bickel, congenital fructose intolerance and Wilson’s disease), (ii) disruption of energy provision (e.g. mitochondrial cytopathies) or (iii) disruption of endocytosis and intracellular transport (e.g. Lowe syndrome, Dent disease and ARC syndrome)”, (Klootwijk et al., 2014).

Table 1. Genetic forms of RFS (Klootwijk et al., 2014)

Gene	OMIM	Disorder	Associated features
Systemic disorders			
<i>GALT</i>	230400	Galactosaemia	Liver dysfunction, jaundice, encephalopathy, sepsis
Multiple nuclear and mitochondrial DNA variants	Multiple	Mitochondrial cytopathies	Usually multisystem dysfunction (brain, muscle, liver, heart)
<i>FAH</i>	276700	Tyrosinaemia	Poor growth, hepatic enlargement and dysfunction, liver cancer
<i>ALDOB</i>	229600	Congenital Fructose Intolerance	Rapid onset after fructose ingestion, vomiting, hypoglycemia, hepatomegaly
<i>CTNS</i>	219800	Cystinosis	Poor growth, vomiting, rickets ± corneal cystine crystals, kidney failure
<i>GLUT2</i>	227810	Fanconi–Bickel syndrome	Failure to thrive, hepatomegaly, hypoglycemia, rickets
<i>OCRL</i>	309000	Lowe's syndrome	Males (X-linked), cataracts, hypotonia, developmental delay
<i>CLCN5</i> , <i>OCRL</i>	300009, 300555	Dent disease I, II	Males (X-linked), hypercalciuria, nephrocalcinosis
<i>ATP7B</i>	277900	Wilson's	Hepatic and neurological disease, Kayser-

		disease	Fleischer rings
<i>VPS33B</i> , <i>VIPAR</i>	208085, 613404	ARC syndrome	Arthrogryposis, platelet abnormalities, cholestasis
<i>HNF4A</i>	125850	MODY1	Neonatal hyperinsulinism, Maturity-onset of diabetes in the young, mutation R76W shows RFS
Isolated RFS?	134600	FRTS1	Glomerular kidney failure
<i>SLC34A1</i>	613388	FRTS2	Phosphaturia dominating
<i>EHHADH</i>	615605	FRTS3	No kidney failure

Recently, it has been described in patients with MODY1 ('maturity-onset diabetes of the young' type 1). Interestingly, only this specific heterozygous mutation, R76W in HNF4A, is associated with a renal phenotype, while other mutations in HNF4A will cause only pancreatic β -cell dysfunction. Three forms genetically were isolated of renal Fanconi syndrome: Fanconi renotubular syndrome (FRTS) 1–3 type. The first one was linked to a locus on chromosome 15; the underlying gene is not yet identified. FRTS1 is also related to progressive chronic kidney disease (CKD). Therefore, it may help understanding the progression mechanism of CKD. The autosomal dominant pattern of inheritance has been described in some families with progressive CKD and RFS phenotype.

FRTS2 is associated with phosphate-wasting where rickets dominates the phenotype. In spite of that, there are elevated levels of 1,25 dihydroxy-vitamin D₃ with some proximal tubules disturbances. Loss of function homozygous mutation of SLC34A1 encoding the phosphate transporter NaPi-IIa was described. Surprisingly, the mutation of SLC34A causes inherited hypophosphataemic rickets with hypercalciuria, given that mutation in SLC34A3, which encodes another phosphate transporter NaPi-IIc in kidney. Depletion of phosphate intracellularly may be the underlying mechanism resulting in an insufficient generation of ATP. A Glycosuria is frequently observed in patients with hypophosphatemic rickets. However, other indicators of proximal tubules dysfunction, i.e. low-molecular weight proteinuria, are normal.

FRTS3, according to (Klootwijk et al., 2014) a report, was not found to be a significant risk factor for CKD development. Additionally, a single locus on chromosome 3 was identified, where a heterozygous missense mutation was found with gene-sequencing within this locus. This gene is called EHHADH, which encodes a peroxisomal bifunctional enzyme (L-PBE) that participated in fatty acid metabolism. This mutation introduces a de novo N-terminal mitochondrial targeting motif (Klootwijk et al., 2014).

Mixed Renal Tubular Acidosis:

It is also known as type 3 RTA (carbonic anhydrase dysfunction). This type is caused by a mutation in the CA-2 gene on 8q22, in autosomal recessive form. This is a rare mutation so some time can be missed due to lack of suspicion. Also, it's a rare mutation in westerns due to infrequent consanguineous marriage (Alsharidi, Al-Hamed, and Alsuwaida, 2015). In this form of RTA impairment of both proximal HCO₃⁻ reabsorption and distal acidification, and more distressingly osteopetrosis, cerebral calcification, and mental retardation occur. The clinical presentation of type 3 RTA, is caused by slower carbonic acid conversion to and from bicarbonate, it seems that also involve direct interaction between CA and the Na⁺/HCO₃⁻ cotransporter or Cl⁻/HCO₃⁻ exchanger (Ring, Frische, and Nielsen, 2005).

Type IV Renal Tubular Acidosis:

In type IV RTA aldosterone resistance or deficiency result in hyperkalemia (Bagga and Sinha, 2007). It follows autosomal inheritance either dominant trait or recessive. The autosomal dominant trait was described in mineralocorticoid receptor gene, which restricted to the kidneys. The autosomal recessive trait was described in epithelia sodium channel that found additionally to the kidney, in the lungs, salivary glands, and colon (Sanjad, 2003). Normally, aldosterone enhances Na⁺ reabsorption and causes a negative intra-tubular potential. The permeability of K⁺ on luminal membrane It also increases and induces basolateral Na⁺/K⁺-ATPase, results in increasing urinary K⁺ losses. As the proton pump is stimulated by aldosterone, the deficiency or resistance is predictable to cause hyperkalemia and acidosis. Ammonia-generation inhibition is another main reason for reducing net H⁺ excretion in type IV RTA because of hyperkalemia. In type IV RTA, pH of the urine can't be more than (5.5), suggesting the ability to establish a maximal H⁺ gradient. Nevertheless, the degree of ammonium excretion is low despite the greatly acidic urine (Bagga and Sinha, 2007).

Gordon's syndrome:

It is an uncommon autosomal dominant disorder typically presented with hyperkalemic acidosis, hypertension due to volume expansion of plasma, and low levels of renin. Recently, it has been suggested that gain of function mutations in the WNK1 and WNK4 kinases genes, may cause enhancing chloride conductance transcellular and paracellular. (Sanjad, 2003).

III. CLINICAL PRESENTATION

Mainly history of polyuria, polydipsia and enjoying salty food are essential in all patients. Children with delayed diagnosis additionally have a failure to thrive, short stature, refractory rickets and deformities of bone because of persistent acidosis. It can present with numerous other unrelated manifestations depending on the underlying systemic disease, type of tubular acidosis, e.g., eye changes in tyrosinemia and hepatic manifestations in cystinosis and with Fanconi syndrome. Collagen vascular disorders and interstitial nephritis can be seen with both distal and proximal RTA. RTA because of obstructive nephropathy will have lived obstructive urological symptoms (Sharma, Gupta and Saxena, 2015).

The most frequent symptom of Distal RTA is metabolic acidosis and nephrolithiasis. Fatigue is a common complaint, probably linked to the metabolic acidosis-induced hyperventilation. Chronic metabolic acidosis patients are disposed to develop osteoporosis. "Metabolic acidosis affects bone by exchanging protons for sodium, potassium, calcium, carbonate, and phosphate". The permanent protons accumulation in bone stimulates both osteoclast growth and osteoclast activity. As a result increases bone resorption, enhancing calcium release from the bone surface and mineral buffers like bicarbonate and phosphate. Finally, this mechanism will result in net loss of bone and hypercalciuria.

Metabolic acidosis also results in enhancing proximal tubular reabsorption of citrate, as a consequence of that is hypocitraturia. Alkaline urine in combination with hypocitraturia and hyperphosphaturia enhances calcium phosphate precipitation resulting in nephrocalcinosis and/or kidney stones. Moreover, patients with distal RTA frequently develop potassium balance abnormalities. Overall, metabolic acidosis will cause hyperkalemia as a consequence of the exchange of protons for intracellular potassium. Though, these patients due to a proton secretion flaw are inclined to waste potassium in urine to preserve electroneutrality over the apical membrane. Notwithstanding wasting of potassium, these patients usually have normal serum potassium levels, as potassium moves from intracellular to extracellular compartment (Santos et al., 2015).

IV. CLINICAL APPROACH TO DIAGNOSIS

"Table 2 summarizes the genetic and molecular basis, as well as the clinical, biochemical, and radiological findings useful to identify the subtype of RTA [1–12]". In this review predominantly tackles with primary types of RTA, which are more often discovered in pediatric patients. Almost all primary RTA types come with an early presentation, on first weeks or months of life. The family history may help diagnosis because of the hereditary transmission of the disease and the higher incidence of some kinds of RTA in certain groups of the population. It should be mentioned that in the kinds of RTA that respect the pattern of autosomal recessive transmission, the parents are carriers and the patient who has the disease being may be the first in the family. (Santos et al., 2015).

In Western countries Type I distal RTA is the most common type of primary RTA. In comparison to that, the variety of pediatric renal diseases in KSA is somewhat different from what reported from western countries. This study suggests more epidemiological studies to understand the nature of these diseases and their incidence (Kari, 2012). Incapable to maximally reduce urine pH, and enhance urinary NH_4^+ excretion in the presence of persistent hypokalemia, metabolic acidosis, early nephrocalcinosis development, and frequently associated with nerve deafness. (Santos et al., 2015).

"Isolated type 2 proximal RTA, caused by a decrease in the renal threshold for HCO_3^- reabsorption in the absence of alterations in the transport of other solutes, is extremely rare. The vast majority of genetic forms of type 2 proximal RTA are found as a component of Fanconi syndrome caused by inborn metabolic diseases (e.g., cystinosis) rather than isolated proximal RTA. The distinctive feature of proximal RTA is the massive waste of HCO_3^- that makes it difficult to achieve and maintain normal bicarbonatemia values in spite of high doses of alkali". When the serum HCO_3^- concentration falls below the renal threshold, bicarbonaturia ceases, and the urine pH becomes acidic. (Santos et al., 2015).

Table 2. AR autosomal recessive; AD autosomal dominant; N normal; ↓ low; ↑ high; NR not reported in the vast majority of published cases; SAO Southeast Asian ovalocytosis; MC mineralocorticoid; PHA pseudohypoaldosteronism; ENaC epithelial sodium channel; WNK with-no-lysine kinase; KLHL Kelch-like; CUL cullin; * PHA type II has also been named as Gordon’s syndrome, familial hyperkalemic, hypertension, Bchloride-shunt^ syndrome and, in children without arterial hypertension, Spitzer–Weinstein syndrome. (Santos et al., 2015).

Clinical and genetic characteristics of the four types of primary renal tubular acidosis (RTA). All forms of primary RTA are characterized by a genetic basis and, biochemically, normal serum aniongap hyperchloremic metabolic acidosis					
RTA Type	Defective Gene	Involved Protein	Inheritance	Clinical, biochemical, and radiological features	Associated extrarenal findings
1	ATP6V1B1	ATP6V1B1	AR	Initial presentation is typically in infants or early childhood with failure to thrive and episodes of vomiting, dehydration, and polyuria; serum potassium low or in the lower limit of normality; calciuria normal or high; hypocitraturia; development of nephrocalcinosis detected by ultrasounds at few weeks of age is the	Severe early deafness
	ATP6V0A4	ATP6V0A4	AR		Late deafness
	SLC4A1	AE1	AR	Variable age of presentation in infancy or childhood; failure to thrive; muscle weakness; serum potassium low or in the lower limit of normality; no reported data on citrate excretion and scarce information on calciuria which has been found normal in some patients; medullary nephrocalcinosis in the majority; frequent rickets and bone deformities	Hemolytic anemia, mainly SAO in Thai population
	SLC4A1	AE1	AD	Presentation in childhood or adulthood; milder manifestations; serum potassium low or normal; no reported data on calcium and citrate excretions; nephrocalcinosis in about half of the patients	Ocular (cataracts, glaucoma and band keratopathy)
2	SLC4A4	NBCe1	AR	Very rare disorder, reported in few families; presentation in infancy or early childhood; growth failure; serum potassium low or normal; calciuria normal; urine citrate not reported (presumably normal); no nephrocalcinosis or urolithiasis	Neurological (mental retardation, familial migraine)
	Unknown	Unknown	AD	Two families reported; presentation in infancy or early childhood; growth failure; serum potassium low or normal; normocalciuria; urine citrate not reported (presumably normal); no nephrocalcinosis or urolithiasis	
3	CA2	Carbonic anhydrase 2	AR	Presentation in infancy or early childhood; growth failure; serum potassium low or normal; levels of calcium and citrate excretions likely depending on the variable degree of proximal and distal components of RTA; nephrocalcinosis in a minority of patient	Osteopetrosis Cerebral calcification after the 2nd year of life and mental retardation High prevalence in Arab population
4	NR3C2	MC receptor	AD	Renal form of primary PHA type 1: presentation in infants, variable severity, with failure to thrive, vomiting and dehydration; hyponatremia, hyperkalemia and high concentrations of serum aldosterone; normal urine citrate and calcium excretion; no nephrocalcinosis	
	SSCNN1A	α subunit of ENaC	AR	Systemic form of primary PHA type I: neonatal presentation severe renal salt wasting, life-threatening hypovolemia, extreme SCNN1B B subunit of ENaC AR hyperkalemia, metabolic acidosis, and markedly elevated plasma renin activity and aldosterone levels	Pulmonary infections
	SCNN1B	B subunit of ENaC	AR		
	SCNN1G	γ subunit of ENaC	AR		
	WNK4	WNK4	AD	Forms of primary PHA type II*: presentation in childhood and	
	WNK1	WNK1	AD	adulthood; hyperkalemia and hypertension with normal glomerular filtration rate, mild acidosis, suppressed plasma renin levels and circulating aldosterone relatively low for the degree of hyperkalemia;	Myalgias, periodic paralysis, and dental abnormalities in a subset of patient
KLHL3	KLHL3	AR OR AR	hypercalciuria in some patients. More severe phenotype and growth impairment in patients with KLHL3 or CUL3 mutations		
CUL3	CUL3	AD			

V. LABORATORY APPROACH TO DIAGNOSIS

- **Basal studies:**

Plasma anion gap (AG):

It has to be the primary biochemical work-up for diagnosing a child with chronic metabolic acidosis. The characteristic of All RTA types is hyperchloremic metabolic acidosis, i.e., normal AG. For the reliable interpretation of plasma AG, calculated as $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$. The AG value signifies the difference between unmeasured cations and unmeasured anions. Factors that can affect AG are: plasma concentrations of albumin, magnesium, calcium, and phosphate (Santos et al., 2015).

Urinary ammonium and pH:

The measurement of NH_4^+ and pH in the study of metabolic acidosis should be in conjunction when the patient is acidotic and same urine sample. A regular kidneys response to metabolic acidosis includes the urine pH decreasing and stimulates production and urinary elimination of NH_4^+ . A normal adult removes about 40 mEq/day of NH_4^+ under a usual Western diet. This quantity is larger in children when assessed on a per-kilogram basis owing to the production of H^+ that results from the new bone formation. Short-term metabolic acidosis outcome is minimum urine pH lower than 5.5, but concentrations of urinary NH_4^+ do not increase maximally, whereas chronic metabolic acidosis results in a pronounced increase of urinary NH_4^+ , which can prevent the maximum decrease of urine pH that gives a thought of free H^+ concentrations. For a precise analysis of urine pH and NH_4^+ values, you should be aware of some factors that might interfere with the normal achievement of a minimum pH without intrinsic renal defects acidification; very diluted urine, (a very low concentration of urinary sodium, and bacterial growth.), (Santos et al., 2015).

Urinary AG:

NH_4^+ in urine measurement is burdensome that is why not so many clinical laboratories do it. In the presence of hyperchloremic metabolic acidosis may be taken into consideration the urinary AG ($\text{Na}^+ + \text{K}^+ - \text{Cl}^-$) as indirect of urinary NH_4^+ excretion index. Urine AG is negative as a result of high concentrations of NH_4^+ that is accompanying with high concentrations of Cl^- . Positive values ($\text{Na}^+ + \text{K}^+ > \text{Cl}^-$) suggest incorrectly low NH_4^+ excretion. Though, some boundaries must be kept in mind, i.e., the association “between urinary AG and NH_4^+ has been shown to be weak in neonates and young infants” (Santos et al., 2015).

Urinary osmolal gap:

AG of urine does not correlate with NH_4^+ when this accompanies other anions than Cl^- excretion. In this case, urinary NH_4^+ can be calculated by urine osmolality $-(2\text{Na}^+ + 2\text{K}^+ + \text{urea} + \text{glucose})$ with urea and glucose concentrations expressed in mmol/l (to convert from mg/dl to mmol/l, divide by 2.8 and 18, respectively). A value higher than 100 mOsm/kg H_2O suggests high NH_4^+ in the urine. With this method, we can use bedside screen for gross urinary NH_4^+ changes in concentration and can be diagnostic in patients with diabetic ketoacidosis or D-lactic acidosis (Santos et al., 2015).

- **Functional tests**

Ammonium chloride load:

Several acidifying agents have been described in the literature, for example, ammonium chloride (NH_4Cl), calcium chloride and arginine hydrochloride, to study the renal response to metabolic acidosis.

Giving of NH_4Cl has been typically considered a main test in the distal RTA diagnosis. Nevertheless, nowadays it is restricted in clinical application since the RTA patients are spontaneously acidotic and poorly tolerated as it causes nausea and vomiting. Infants can be given 75 mEq/ m^2 as a single dose of NH_4Cl diluted via nasogastric tube, while in children usually has been given 150 mEq/ m^2 over one hour in gelatin-coated capsules P.O, collecting urine over the following 6–8-h period. The test must be confirmed by that the dose of NH_4Cl induces metabolic acidosis: blood tCO₂ as a minimum lower than 18 mmol/l in infants and lower than 21 mmol/l in older children. Normally the urine pH falls below 5.5, and urinary NH_4Cl raises up to 57 ± 14 (mean \pm SD) $\mu\text{Eq}/\text{min}/1.73\text{ m}^2$ in 1–16 months infants and 80 ± 12 $\mu\text{Eq}/\text{min}/1.73\text{ m}^2$ in 7–12 years. In connection with NH_4^+ excretion, it is low in children with type 1, 3 and type 4 RTA and it is likely to be

normal in pure type 2 RTA children (Santos et al., 2015).

Bicarbonate load:

This test allows us to calculate the fractional excretion (FE) of HCO_3^- , when the plasma concentration of HCO_3^- is normal and the difference of urine-to-blood (U-B) pCO_2 , when the urine becomes more alkaline than the blood. "FE of HCO_3^- is controlled by saving the urine sample under mineral oil and using the formula $(\text{Urine } \text{HCO}_3^- \times \text{Plasma creatinine} \times 100) / (\text{Plasma } \text{HCO}_3^- \times \text{Urine creatinine})$ ".

In proximal RTA, excrete considerable amounts of HCO_3^- when plasma HCO_3^- is beyond the renal threshold, while in distal RTA patients, the bicarbonaturia is typical except if there is a transient proximal HCO_3^- lose, as found in some infants with HCO_3^- FE range from 6 - 15% in the existence of normal plasma HCO_3^- accomplished during intravenous infusion of sodium bicarbonate. In patients with primary type 3 RTA (mainly due to CA deficiency), the FE of HCO_3^- values with normal serum bicarbonate rely on the severity of the proximal HCO_3^- reabsorption impairment. In type 4 RTA; HCO_3^- FE in the setting of normal bicarbonate level is generally being between 5 - 10 %.

Perform this test by administering 4 mEq/kg of sodium bicarbonate P.O. However, in a large percentage of patients, the dose does not normalize plasma HCO_3^- . These patients need larger doses of oral bicarbonate, or I.V infusion of a 3.75 % solution of sodium bicarbonate at rates changing from 0.3 to 0.8 ml/min to cause an increase of 2–3 mEq/l/h of plasma HCO_3^- and to reduce the expansion of extracellular volume. Even if a normal plasma concentration of HCO_3^- is not reached, it is an evidence of defective proximal reabsorption when plasma HCO_3^- is below normal levels with extensive bicarbonaturia.

The measurement of pCO_2 in urine when the pH of the urine is greater than the pH of blood is a sensitive index of H^+ secretion of distal nephron, due to a chemical gradient. Within the lumen of tubules, H^+ merge with HCO_3^- to form H_2CO_3 , which as consequent of CA deficiency in the luminal side, dehydrates gradually into CO_2 and water. The negative relationship of surface-to-volume restricts the diffusion of CO_2 out of the lumen that leads to high pCO_2 in the final urine. The pH is above 7.6 and HCO_3^- concentration higher than 80 mEq/l. In patients with type 1 RTA, the value of U-B pCO_2 is about 0 or even negative, whereas it is likely to be normal in type 2 and 4 RTA, in normal individuals the gradient of U-B pCO_2 should be greater than 20 mmHg. In patients with osteopetrosis and type 3 RTA, acidification is defective, and in alkaline urine U-B pCO_2 is low (Santos et al., 2015).

Acetazolamide administration:

Inhibition of CA-2 by acetazolamide causes decreasing of HCO_3^- reabsorption at the proximal tubule which leading to enhance bicarbonaturia. The maximum pH of the urine was reached more quickly with acetazolamide than with sodium bicarbonate (160 vs. 116 min); acetazolamide was more acceptable and tolerable. The conclusion basis on these results, that oral acetazolamide at a dose of 15–20 mg/kg, can substitute sodium bicarbonate in the estimation of U-B pCO_2 . Interestingly, following administration of acetazolamide, urinary pH and HCO_3^- excretion have been found to be same in patients with CA deficiency and healthy individual (Santos et al., 2015).

Furosemide test:

The $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter is blocked by furosemide in the thick ascending limb of the loop of Henle, therefore increasing NaCl delivery to the distal segments of the nephron. Cortical collecting duct increases Na^+ reabsorption and develops a negative voltage, which stimulates the secretion of H^+ and K^+ to urine. Therefore, furosemide administration to normal persons results in urine acidification associated with a kaliuretic response and increasing NH_4 excretion. The dose of furosemide generally is 1 mg/kg either I.V or P.O, and collects urine samples over a period of 4 h. The pH of urine falls lower than 5.3 whereas urine NH_4^+ and K^+ excretion increase 2–3 X. Administration of Furosemide intravenously can cause unusual increasing plasma renin activity and aldosterone concentration, whereas their activities do not significantly increase when the diuretic is administered by mouth. As a result of low sodium delivered or impaired reabsorption distally, the patients have decreased of H^+ secretion distally, and will normally respond to the furosemide test, whereas primary distal RTA patients "do not correct the acidification defect or the low excretion" of NH_4^+ (Santos et al., 2015).

Furosemide + fludrocortisone test:

The simultaneous administration of furosemide and fludrocortisone has been proposed to replace administration of NH_4Cl

in the diagnosis of distal RTA. “The advantage of adding fludrocortisone to furosemide is that the mineralocorticoid action stimulates reabsorption of sodium by the principal cells of the collecting duct a few minutes after its administration, thus facilitating the secretion of H⁺ and the decrease of urinary pH. The test is better tolerated than the NH₄Cl load and causes a decrease of urinary pH and an increase of urinary NH₄⁺ in a shorter period of time. Oral administration of 40 mg of furosemide and 1 mg of fludrocortisone to healthy adults acidifies the urine to a pH <5.3 and increases NH₄⁺ excretion up to 85±23 μEq/min (mean ± SE), whereas patients with distal RTA fail to acidify their urine to pH <5.3 and do not significantly increase NH₄⁺ excretion over the basal values” (Santos et al., 2015).

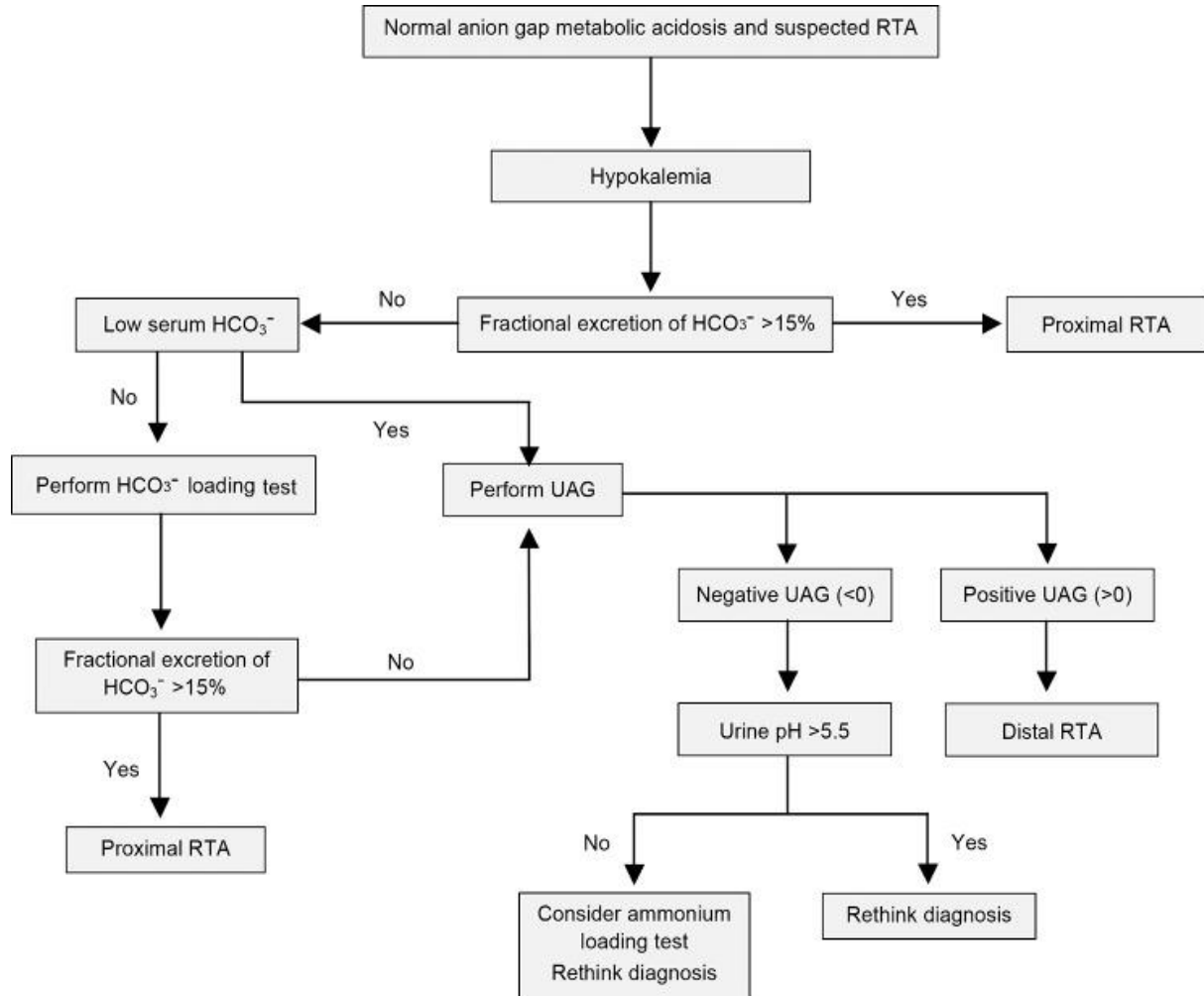


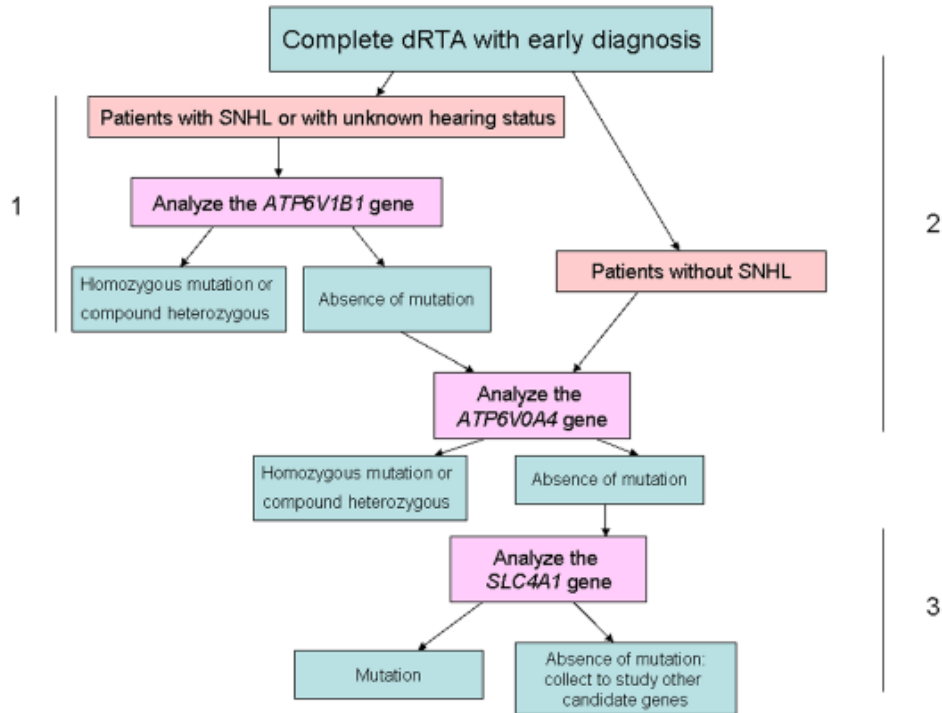
Figure5. Suggested algorithm for suspected renal tubular acidosis (RTA) in patients with non-anion gap metabolic acidosis and hypokalemia. HCO₃⁻, bicarbonate; UAG, urine anion gap (Yaxley, J., & Pirrone, C. 2016).

VI. MOLECULAR DIAGNOSIS

Mostly done with distal RTA. In the suspected cases that present mostly with feeding difficulties, dehydration, and failure to thrive, non-gap metabolic acidosis and inability to renal acidification. Additional common findings were hypokalemia, diffuse nephrocalcinosis, rickets, and total hearing loss (Elhayek et al., 2013).

Mutation detection: To Approach patients with mentioned sing and symptoms we should analyze the responsible genes. First, investigate ATP6V1B1 gene, and according to a case study, mutations were detected in homozygosis. Subsequently, investigate the ATP6V0A4 gene in the absence of ATP6V1B1 mutation or cases with no hearing loss. Finally screen SLC4A1 gene mutation. Between the ATP6V1B1, and ATP6V0A4 genes mutation there are no phenotypically difference apart from presence or absence of hearing loss. This mutation follows AR pattern (Elhayek et al., 2013).

According to some authors' recommendation, any pediatric patients present with early SNHL should be screened for ATP6V1B1 mutation, while the delayed type associated with ATP6V0A4 (Elhayek et al., 2013).



“Fig.6 Algorithm followed for the genetic analysis. 1, 2 and 3 (the different steps of the analysis). (Elhayek et al., 2013)

VII. MANAGEMENT

Distal RTA:

The advantages of acidosis correction including children normal growth restoration in, renal potassium wasting and hypokalemia become less in distal RTA, nephrocalcinosis stabilization, decrease calcium stones recurrence in the kidney, and perhaps less osteoporosis, and rickets or osteomalacia in distal RTA and proximal RTA respectively. An adult who consumes a western diet generates a relatively fixed amount of acid that is excreted in the form of ammonium via kidneys. A patient with distal RTA reduces ammonium excretion. Thus hydrogen retained with urinary loss of bicarbonate has to be compensated by alkali intake (sodium bicarbonate or sodium citrate).

Children may require approximately 4 to 8 meq/kg per day because they often have larger losses of bicarbonate, and the rapidly thriving children produce an additional load of acid.

An indication of potassium citrate administration is when in spite of serum bicarbonate correction hypokalemia continues. Also in certain patients who have hypercalciuria and calcium stone, potassium citrate may be efficient, because, in systemic acidosis, reabsorption of citrate in proximal tubules is increased. Thus urinary citrate is decreased, together with calcium loss into the alkaline urine; result in increasing the risk of calcium phosphate stones and, nephrocalcinosis in certain patients. Citrate in the urine increases as a result of decreasing acidosis that inhibits calcium salts crystallization. Sodium salts can advance the excretion of calcium and deteriorate stone illness.

In the case of paralytic hypokalemia, the correction of potassium is the thing we focus on not the metabolic acidosis. That is why in such a case the administration of potassium in glucose and bicarbonate lacking solution. (Emmett, and Biff F, 2017)

Proximal RTA:

Proximal RTA patients present with acidemia, adjustment of acidemia will enhance skeletal growth and restorative of rickets in children or osteomalacia, if present. In few patients decrease reabsorption of phosphate proximally, and reduce vitamin D activation lead to hypophosphatemia. Therefore, supplementation of phosphate and vitamin D together are required in order to bring the concentration of serum phosphate to the normal level and inverse the metabolic disease of bone.

Metabolic acidosis is more challenging in proximal than distal RTA, because as we increase the concentration of serum

bicarbonate as that increase the filter load on proximal tubules that can lead to bicarbonaturia. That is why here we need more alkali than distal one, about 10 to 15 meq/kg per day to compensate the loss of bicarbonate. Furthermore, bicarbonaturia increases water and sodium in distal nephrons, which can increase potassium loss, bicarbonate itself, exacerbates the loss by its negative charge. Alkali substitute has to be potassium salt (potassium citrate).

Thiazide diuretic can be given too if the patient can't tolerate a large dose of alkali or inefficient. It works by mildly deplete the volume that can promote the proximal reabsorption of sodium and as a result bicarbonate too. (Emmett, and Biff F, 2017)

Type IV RTA:

“Proper treatment depends on the cause” of the hormone disturbance. For instance, Patients with aldosterone deficiency should undergo substitution therapy (with 0.05 to 0.2 mg/day of fludrocortisone) to improve the hyperkalemia and.

In hyporeninemic hypoaldosteronism patients', fludrocortisone is efficient too. The dosage usually is 0.2 to 1 mg/day to correct the potassium to the normal level. The higher dose than primary insufficiency of adrenal suggests renal resistance to aldosterone.

Regardless of that, fludrocortisone is not frequently given in hyporeninemic hypoaldosteronism since many patients come with hypertension and/or edema, which can be aggravated by replacement of mineralocorticoid. In setting, a diet of a low potassium and, if needed, a thiazide or loop diuretics commonly used to control hyperkalemia (Young, 2017).

VIII. ASSOCIATED DISEASES WITH RENAL TUBULAR ACIDOSIS

Food allergy IgA, and IgG4 deficiency:

A repeated upper respiratory tract infections accompanied by gastrointestinal symptoms found in patients with selective IgA and IgG4 deficiencies. Food allergy was established by an oral test to cow's milk, egg, soy, corn, and wheat additional to IgE levels together with the patch test. IgA deficiency criteria were, if serum levels lower than 5 mg/dl, IgG4 levels lower than the percentile defined according to the age of the patient. Renal tubular acidosis considered if a HCO₃ level is lower than 21 electrolyte and urinary criteria. About 96% of patient with IgA IgG4 deficiency have distal RTA. Pathomechanism, allergen is the trigger of the acidosis (Estrada-Reyes, Maciel and Medeiros-Domingo, 2011)

Sjogren syndrome:

Is chronic autoimmune disease of unknown etiology that affects mainly exocrine glands, and others too like, liver, kidney or lungs (Bogdanović et al., 2012). It is hard to diagnose the Sjogren syndrome in childhood because it does not fulfill the criteria, which successfully used for the adult. (Agarwal, Kumar and Gupta, 2015). It is typically presented with recurrent parotid gland swelling. Interestingly, pathological and laboratory signs are identical to those found in adults: “hypergammaglobulinemia, characteristic lymphocytic infiltration of the exocrine glands, positive anti-SSA-A and/or anti-SS-B antibodies, elevated erythrocyte sedimentation rate, and ANA of the spotted type.” (Bogdanović et al., 2012)

Renal involvement in primary Sjogren syndrome includes primarily tubule-interstitial nephritis (TIN) that might manifest as defect concentrating ability, nephrocalcinosis, distal renal tubular acidosis, or rarely, proximal RTA or Fanconi syndrome. The immune complex glomerulonephritis of renal involvement is an infrequent thing that may appear in the course of the disease later and which may develop to renal failure.

Treatment of Sjogren syndrome-associated TIN often includes corticosteroids and/or immunosuppressive drugs for certain duration of time. Patients need permanent supplementation of electrolytes is necessary for growth preservation and/or to complications prevention. The outcome of long-term renal involvement in pediatric primary Sjogren syndrome is mostly good, but not always. (Bogdanović et al., 2012)

Celiac Disease:

Celiac disease (CD) is an autoimmune disorder because of gluten and similar prolamins sensitivity. It is elicited in genetically susceptible persons who have HLA-DQ2 or DQ8 haplotypes. Characterized by gluten-enteropathy (abdominal distension, diarrhea, anorexia, abdominal pain, vomiting, mouth ulcers, constipation and increase appetite), severe acute malnutrition and specific antibodies (IgA anti tissue Transglutaminase) the last one used for diagnosis of CD (Beniwal, Ameta and Chahar, 2017). A reported case of CD patient came with metabolic acidosis, hypokalemia, and alkaline urine. Further investigation has been done which favored the diagnosis of distal RTA. Furthermore, poor growth and delayed

puberty lead to investigate more that revealed elevation of TSH, low T4, and positive anti-thyroperoxidase (anti-TPO) antibodies, a patient was diagnosed with Hashimoto thyroiditis and initiate thyroxin supplementation (Satapathy, Mittal, and Jain, 2016).

Glucose-Galactose malabsorption:

It is rare genetic disorder follows an autosomal recessive pattern in SGLT1 co-transporter gene. In the intestine, unabsorbed glucose and galactose accumulate and leads to osmotic diarrhea and dehydration in first days of life. This can be lethal unless the diet is free of glucose and galactose = (lactose). This condition associated with hypercalcemia, dehydration and metabolic acidosis, which can lead to nephrocalcinosis. Hypercalcemia is due to increase absorption in the ileum, as a result of non-hydrolyzed lactose, and metabolic acidosis. Although the lactose-free diet helps to relieve the symptoms, some patient still have metabolic acidosis, and hypercalcemia persists. Normal plasma anion gap and positive urinary anion gap as a result of reduced excretion of ammonium in urine, suggesting the presence of renal tubular acidosis (El-Naggar et al., 2005).

IX. CONCLUSION

Renal tubular acidosis is an uncommon disease of childhood may be because of under-reporting. It may come as inherited or acquired form. The inherited form is rarer than the acquired one, but the inherited form is more common in children than acquired. The RTA is classified from 1 to 4 in which 1 is an exclusively distal type, 2 is proximal, 3 is mixed of the 1 and 2, and 4 due to aldosterone disturbances either deficiency or resistance of renal parenchyma. The pattern of inheritance is varied from autosomal dominant to recessive, and in some cases, even X-linked can be seen as in Fanconi syndrome. Usually the autosomal dominant is more common than the recessive and that is right as in western countries, but due to the consanguineous marriage as in the Arab nation, the autosomal recessive forms are more common. It is now well known that genetic mutation can lead to some enzymatic deficiency that manifests as RTA. Up to now, there are three well-known genes associated with RTA (ATP6V1B1, ATP6V0A4, and SLC4A1). But due to an association of some autoimmune disease with RTA, autoimmunity as pathomechanism is also considered. When RTA suspected like recurrent renal stone, growth retardation or unexplained hyperkalemia, the patient should undergo several basal (anion gap) and functional (bicarbonate load) tests and even genetic test in case of family history. Appropriate Treatment is according to the type.

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