Renal Tubular Acidosis Type 1: Distal Renal Tubular Acidosis (dRTA) in Children

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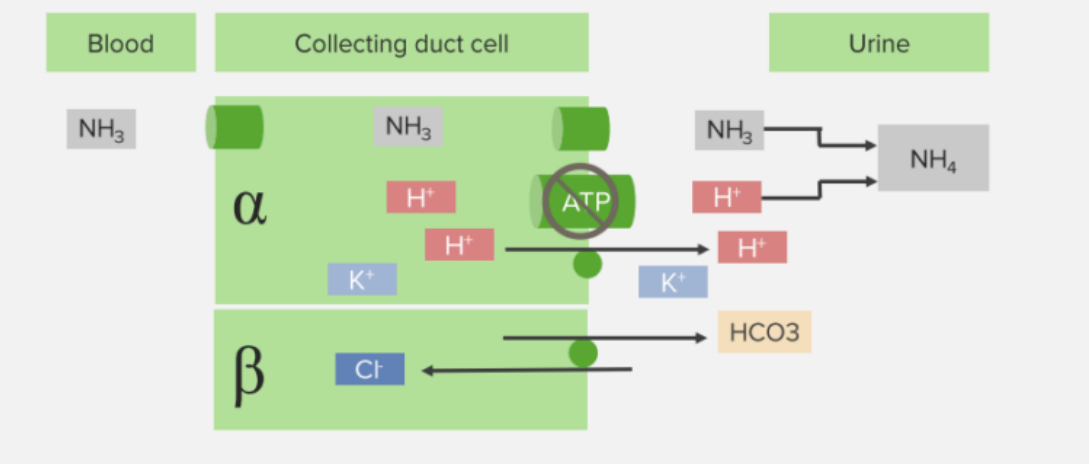
Renal tubular acidosis (RTA) type 1, also called distal renal tubular acidosis (dRTA) is characterized by hyperchloremic metabolic acidosis, hypokalemia, hypercalciuria, and hypocitraturia. Its etiology varies and includes sporadic, hereditary, and acquired forms. RTA type 1 should be differentiated from other forms of RTA and other causes of metabolic acidosis. Long-term alkali therapy is the mainstay of treatment. In this article, etiology, pathophysiology, symptoms, diagnosis, differential diagnosis, treatment, and prognosis of renal tubular acidosis type 1 are reviewed.



Definition

Distal RTA is the classic form of renal tubular acidosis also called renal tubular acidosis type 1. All forms of renal tubular disorders are characterized by hyperchloremic metabolic acidosis. Distal RTA results from the failure of net renal acid excretion, usually from an inability to excrete H^+ ions into lumen of nephron. Due to the failure of acid secretion urine, pH is maintained above 5.3.

Epidemiology of Distal Renal Tubular Acidosis

Primary or hereditary forms of distal RTA usually present in infancy or childhood, while secondary forms present during adulthood. Inherited disorders are much rarer than acquired forms, especially in western populations. Hereditary distal RTA occurs more commonly in parts of the world with high rates of parental consanguinity. The exact prevalence of distal RTA is unknown.

Etiology of Distal Renal Tubular Acidosis

Primary causes

- Sporadic forms
- Inherited forms:
    - Autosomal recessive: defects in HCO_3^-/Cl^- exchanger or H^+ ATPase
    - Autosomal dominant: defect in HCO_3^-/Cl^- exchanger (*SLC4A1* gene on chromosome 17)
- Inherited syndromes: Marfan syndrome (autosomal dominant disease of connective tissue), Wilson disease (too much copper in the body's tissues), Ehlers-Danlos syndrome, Fabry's disease, and hereditary elliptocytosis
- Autoimmune disorder: Sjögren syndrome (tears and saliva-producing glands are destroyed)
- Familial hypercalciuria

Secondary causes

- Urologic causes: obstructive uropathy, vesicoureteral reflux
- Intrinsic renal causes:
    - Nephrocalcinosis: hyperparathyroidism, hypervitaminosis D, milk-alkali syndrome, hyperoxaluria, idiopathic hypercalciuria, etc.
    - Interstitial nephritis, pyelonephritis, sickle cell nephropathy, medullary sponge kidney, transplant rejection
- Systemic diseases: systemic lupus erythematosus, primary biliary cirrhosis, Sjögren's syndrome
- Drugs:
    - Hypergammaglobulinemic states: myeloma, amyloidosis, cryoglobulinemia
    - Amphotericin B, lithium, NSAIDs, cyclophosphamide, ifosfamide, cisplatin, foscarnet
- Other: hepatic cirrhosis, chronic active hepatitis, idiopathic pulmonary fibrosis, thyroiditis, HIV-associated nephropathy

Conditions associated with voltage defect distal RTA

- Decreased distal delivery of Na^+—hypovolemic states, Gordon syndrome (pseudohypoaldosteronism 2)
- Decreased distal reabsorption of Na^+:
    - ENaC defect: pseudohypoaldosteronism 1, drugs (amiloride, triamterene, trimethoprim, pentamidine)
    - Na^+/K^+ ATPase defect—cyclosporine
    - Lupus nephropathy, sickle cell nephropathy, chronic transplant rejection, methicillin

Pathophysiology of Distal Renal Tubular Acidosis

Molecular contribution to inherited dRTA

Important renal mechanisms for maintaining acid-base homeostasis include the reabsorption of filtered HCO_3^- and the excretion of nonvolatile acids. Normally 85–90% of

HCO_3^- is reabsorbed in proximal tubules, and distal segments cause acidification of urine by the reclamation of remaining HCO_3^- and by active secretion of H^+ in the form of titratable acid, $NH4^+$, and free ions. α-intercalated cells of collecting ducts contain H^+ ATPase and basolateral anion exchanger type 1 (AE1), while **β-intercalated cells** contain H^+ ATPase and $Cl–/HCO_3^-$ exchanger (pendrin).

Inherited forms of distal RTA are usually due to a defect in HCO_3^-/Cl^- anion exchanger or in H^+ATPase.

Pathophysiology of type 1 RTA may involve a secretory defect (most common) or a non-secretory defect (gradient defect, buffer defect, or voltage defect).

1) Secretory defect

In a secretory defect, there is a failure to secrete H+ by intercalated cells, possibly due to defective H^+ ATPase, H^+/K^+ ATPase, or HCO_3^-/Cl^- exchanger. This type of RTA is also called classic distal RTA or rate-limiting RTA.

2) Non-secretory defect

A- Gradient defect

Gradient defect distal RTA is characterized by an inability to maintain the gradient due to back-diffusion of the secreted H^+, which may result from the abnormal permeability of the membrane or defective cell junctions. This defect is also called a back-leak defect. A classic example is distal RTA caused by **amphotericin B**.

B- Buffer defect

Buffer defect distal RTA is characterized by decreased delivery of NH_3 to the distal collecting tubule that results in decreased buffering capacity. This type of RTA is also called low buffer type distal RTA. Examples are distal RTA associated with **nephrocalcinosis** and **chronic interstitial nephritis**.

C- Voltage defect

Voltage defect distal RTA is characterized by a dysfunction of principal cells that result in a loss of luminal electronegativity and impaired secretion of H^+ by the intercalated cell. The principal cell dysfunction may be caused by a defective ENaC channel or by drugs affecting the function of ENaC. Reduced H^+ secretion is associated with increased reabsorption of K^+; hence, this type of distal RTA is associated with hyperkalemia (hyperkalemic type 1 RTA). Examples of this type of distal RTA are obstructive nephropathy, sickle cell nephropathy, salt-losing congenital adrenal hyperplasia, and certain drugs.

4) Incomplete distal RTA

Incomplete distal RTA is considered a milder form or a variant of distal RTA. It is characterized by normal serum HCO_3^-, but patients have an inability to acidify urine due to defective tubular secretion of acid. Hypercalciuria and hypocitraturia are present, and there is increased ammoniagenesis to maintain net acid excretion.

Symptoms of Distal Renal Tubular Acidosis

Important symptoms of distal RTA are:

- **Nephrolithiasis**: Calculi formation in the kidney and/or nephrocalcinosis may be present. Nephrocalcinosis is usually irreversible and may lead to polyuric chronic renal failure, while nephrolithiasis occurs later and can be prevented by alkali therapy.
- **Bone demineralization**: Bone disease (osteopenia or osteomalacia) seen in distal RTA results from chronic acidosis, which causes bone matrix calcium resorption. Impaired growth hormone release may contribute to growth retardation in children with distal RTA. Vitamin D deficiency causes rickets in children.
- **Hyperchloremic metabolic acidosis**: Hyperchloremic metabolic acidosis with a normal serum anion gap and hypokalemia. In distal RTA, because of a lack of H+ in tubular lumen, bicarbonate is lost in urine, which results in increased chloride absorption, causing hyperchloremia.
- **Hypokalemia**: Low levels of K^+ cause proximal muscle weakness, fatigue, constipation, or paralysis.
- **Hypercalciuria** (urinary stone formation): Because of a high concentration of HCO_3^-, increased K^+ secretion occurs distally as a compensatory response to decreased H^+ secretion, which causes hypokalemia.
- Hypercalciuria can often lead to **nephrocalcinosis or nephrolithiasis**. The risk of nephrocalcinosis/nephrolithiasis is further increased by high urine pH and hypocitraturia, which is caused by proximal citrate reabsorption induced by acidosis.
- **The urine pH is abnormally elevated** despite systemic acidosis. Urine $NH4^+$ excretion is low.
- Impairment of proton secretion in the distal nephron to a degree beyond that expected for the patient's renal function may be seen.
- Incomplete distal RTA clinically presents with renal stones or unexplained osteoporosis.
- Inherited disorders (autosomal recessive) are associated with sensorineural hearing loss.

Other symptoms include polyuria, polydipsia, and growth retardation. Symptoms presenting in the first years of life may include poor feeding, vomiting, and failure to thrive. Distal RTA seen in childhood is usually primary or inherited.

Diagnosis of Distal Renal Tubular Acidosis

The hallmark of RTA is non-anion gap metabolic acidosis (NAGMA) or hyperchloremic metabolic acidosis. Important laboratory findings in distal RTA are low serum HCO_3^-, hyperchloremia, hypokalemia (except in hyperkalemic type distal RTA), hypercalciuria, hypocitraturia, and low urinary $NH4^+$. Serum calcium, serum phosphate, and urinary phosphate are normal.

Measurement of urinary $NH4^+$ by formaldehyde titration should be performed. Measurement of urinary Na+ is important, as low urinary sodium is associated with a voltage-dependent acidification defect. This measurement method is cumbersome; hence, the urinary anion gap is calculated as an indirect method to approximate urinary $NH4^+$ excretion.

1. **Urine anion gap (UAG)** is helpful to differentiate between renal and non-renal causes of NAGMA.

UAG = $[NA^+]Ur + [K^+]Ur – [Cl^-]Ur$

- UAG is positive in normal conditions and in RTA. When urinary excretion of $NH4^+$ is high (as in extrarenal bicarbonate loss), UAG becomes negative.
- Interpretation of UAG is invalid in conditions associated with a significant presence of unmeasured ions (lithium, ketones, acetylsalicylate, etc.) in urine or when urine pH is more than 6.5 (due to significant excretion of bicarbonate in urine).

1. **Urine osmolal gap (UOG)** helps to differentiate between renal and non-renal causes of NAGMA when there is a significant presence of other anions.

UOG = $[Osm]Ur – (2[Na^+]Ur + 2[K^+]Ur + [Urea]Ur + [Glu]Ur)$

- When there is an increased secretion of $NH4^+$, UOG equals or is greater than 100 mmol/L, the value of UOG/2 is roughly equal to $[NH4^+]Ur$. However, UOG is invalid in conditions associated with a significant presence of unmeasured osmolals like lithium.
- Urine pH more than 5.5 suggests renal acidification defect when pH is measured in a fresh, early morning urine sample. Remember that type II RTA and type IV RTA can present with urine pH < 5.5.

1. **Ammonium chloride loading test** is the most commonly used acid-loading test, in which 0.1 g/kg NH4Cl is given orally to induce systemic acidosis and ABG and urine pH are monitored hourly. Normally, urine pH should fall below 5.5 in the presence of systemic acidosis. Urine pH more than 5.5 in the presence of systemic acidosis suggests a distal acidification defect. The ammonium chloride loading test may cause nausea, vomiting, gastric upset, etc. As it is contraindicated in chronic liver disease, calcium chloride is used to induce acidosis.

1. **Sodium bicarbonate loading test** is performed by oral or intravenous administration of sodium bicarbonate to alkalinize urine (urine pH > 7.5). Normally, in the presence of steady-state serum bicarbonate (23–25 mEq/L) and alkaline urine, urine CO_2 is more than 70 mm Hg, urine-to-blood pCO_2 gradient (U-B pCO_2) is more than 20 mm Hg, and fractional excretion of bicarbonate ($FEHCO_3$) is less than 5%.

$FEHCO_3$ (%) = (urine bicarbonate x plasma creatinine) / (plasma bicarbonate x urine creatinine) x 100

In classic distal RTA, urine pCO_2 is less than 50 mm Hg, U-B pCO_2 is less than 10 mm Hg, and $FEHCO_3$ is less than 5% on the sodium bicarbonate test. In voltage defect distal RTA, urine pCO_2 is more than 70 mm Hg, U-B pCO_2 is more than 20 mm Hg, and $FEHCO_3$ varies from 5–10%.

Differential Diagnoses of Distal Renal Tubular Acidosis

- Other types of RTA
- Other causes of NAGMA
    - Chronic renal failure
    - Extrarenal bicarbonate loss–diarrhea, intestinal fistula, etc

- Ketoacidosis
- Lactic acidosis
- Exogenous administration of Cl^--rich solutions
- Parenteral nutrition
- Drug toxicity

Urinalysis: The color change on the dipstick provides information about the level of acid in the urine. Some types of kidney stones are more prone to develop in alkaline urine, and others are more likely to form in acidic urine. Monitoring the urine pH may be helpful in preventing the formation of kidney stones.

Therapy of Distal Renal Tubular Acidosis

Chronic alkali supplementation is the mainstay of treatment. Correcting acidosis is important for improving growth in children, decreasing the incidence of **hypokalemia** and nephrocalcinosis/**nephrolithiasis**, and slowing the progression of chronic renal disease. The therapeutic goal is to maintain normal serum bicarbonate level (22–24 mEq/L).

Simple alkali replacement (1–3 mmol/kg per d of citrate or bicarbonate orally) is sufficient to reverse most of the biochemical abnormalities and associated bone disease in both dominant and recessive dRTA, leading to the resumption of normal growth.

Children with severe metabolic acidosis (serum bicarbonate < 12 mEq/L) are given intravenous bicarbonate after calculation of the required dose. Half of the required dose is administered over 8 hours, and the remaining half is administered over the next 24 hours. The required dose is calculated using the following formula:

> **required dose = desired change in serum bicarbonate x body weight (kg) x 0.6**

In patients with serum bicarbonate between 12–17 mEq/L, oral bicarbonate therapy is sufficient. Sodium and/or potassium bicarbonate or citrate is used for treatment. **Shohl's solution** (1 mEq/mL base contains citric acid and sodium citrate) is preferred over sodium bicarbonate.

The requirement for alkali decreases with age and ranges from 5–8 mEq/kg/day in infants, 3–4 mEq/kg/day in children, and 1–2 mEq/kg/day in adults. As secretion of growth hormone peaks during sleep, the larger dose of alkali is administered at bedtime in children.

A low sodium diet and thiazide diuretics are useful to reduce bicarbonate wasting. Normal serum HCO_3^- and optimum growth indicate appropriate treatment. As there is an inverse relationship between plasma HCO_3^- and urinary calcium, the absence of hypercalciuria indicates good control of metabolic acidosis. Annual abdominal sonography should be performed to monitor for nephrocalcinosis and nephrolithiasis.

Progression and Prognosis of Distal Renal Tubular Acidosis

Complications

Complications of dRTA include severe hypokalemia, leading to cardiac arrhythmias and paralysis, nephrolithiasis, and nephrocalcinosis. Profound hypokalemia aggravated by

hyperemesis gravidarum, recurrent urinary tract infection (UTI), and ureteric obstruction leading to renal failure. A woman with dRTA may also suffer from adverse pregnancy-related outcomes. Alternation in acid-base homeostasis occurs during normal pregnancy; however, severe dRTA in pregnant women causes UTI or renal failure.

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Notes