Renal Tubular Acidosis Type 1: Distal Renal Tubular Acidosis in Children

Definition

Distal renal tubular acidosis (dRTA) is the classic form of renal tubular acidosis, which is 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 due to an inability to excrete H⁺ ions into the lumen of the nephron. Due to the failure to secrete acid in the urine, the pH is maintained above 5.3.

Epidemiology of dRTA

Primary or hereditary forms of dRTA 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 dRTA occurs more commonly in parts of the world with high rates of parental consanguinity. The exact prevalence of dRTA is unknown.
Etiology of dRTA

Primary causes

- Sporadic forms
- Inherited forms:
  - Autosomal recessive: defects in $\text{HCO}_3^-/\text{Cl}^-$ exchanger or $\text{H}^+$ ATPase
  - Autosomal dominant: defect in $\text{HCO}_3^-/\text{Cl}^-$ exchanger ($\text{SLC4A1}$ gene on chromosome 17)
- Inherited syndromes: Marfan’s syndrome (autosomal dominant disease of connective tissue), Wilson’s disease (too much copper in the body’s tissues), Ehlers-Danlos’s syndrome, Fabry’s disease, and hereditary elliptocytosis
- Autoimmune disorder: Sjögren’s 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 a voltage defect in dRTA

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

Pathophysiology of dRTA

Molecular contribution to inherited dRTA

Important renal mechanisms for maintaining acid–base homeostasis include the reabsorption of filtered $\text{HCO}_3^-$ 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 the remaining HCO$_3^-$ and by active secretion of H$^+$ in the form of titratable acid, NH$_4^+$, and free ions. The $\alpha$-intercalated cells of collecting ducts contain H$^+$ ATPase and basolateral anion exchanger type 1 (AE1), while the $\beta$-intercalated cells contain H$^+$ ATPase and Cl$^-$/HCO$_3^-$ exchanger (pendrin).

Inherited forms of dRTA are usually due to a defect in the HCO$_3^-$/Cl$^-$ anion exchanger or in H$^+$ATPase.

The 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 the intercalated cells, possibly due to a defective H$^+$ ATPase, H$^+$/K$^+$ ATPase, or HCO$_3^-$/Cl$^-$ exchanger. This type of RTA is also called classic dRTA or rate-limiting RTA.

2) Non-secretory defect

A: Gradient defect

Gradient defect dRTA 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 dRTA caused by amphotericin B.

B: Buffer defect

Buffer defect dRTA is characterized by a decreased delivery of NH$_3$ to the distal collecting tubule, which results in a decreased buffering capacity. This type of RTA is also called low-buffer type dRTA. Examples are dRTA associated with nephrocalcinosis and chronic interstitial nephritis.

C: Voltage defect

Voltage defect dRTA is characterized by a dysfunction of principal cells that results 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$^+$; therefore, this type of dRTA is associated with hyperkalemia (hyperkalemic type 1 RTA). Examples of this type of dRTA are obstructive nephropathy, sickle cell nephropathy, salt-losing congenital adrenal hyperplasia, and certain drugs.

Incomplete dRTA

Incomplete dRTA is considered a milder form or a variant of dRTA. It is characterized by normal serum HCO$_3^-$, but patients have an inability to acidify urine due to the defective tubular secretion of acid. Hypercalciuria and hypocitraturia are present, and there is increased ammoniagenesis to maintain the net acid excretion.
Symptoms of dRTA

Important symptoms of dRTA are as follows:

- **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 dRTA results from chronic acidosis, which causes bone matrix calcium resorption. Impaired growth hormone release may contribute to growth retardation in children with dRTA. Vitamin D deficiency causes rickets in children.

- **Hyperchloremic metabolic acidosis**: In hyperchloremic metabolic acidosis, there is a normal serum anion gap and hypokalemia. In dRTA, because of a lack of H⁺ in the tubular lumen, bicarbonate is lost in the urine, which results in increased chloride absorption, causing hyperchloremia.

- **Hypokalemia**: Low levels of K⁺ cause proximal muscle weakness, fatigue, constipation, or paralysis.

- **Hypercalciumia** (urinary stone formation): Because of a high concentration of HCO₃⁻, increased K⁺ secretion occurs distally as a compensatory response to decreased H⁺ secretion, which causes hypokalemia.

- **Hypercalciumia** can often lead to **nephrocalcinosis or nephrolithiasis**. The risk of nephrocalcinosis/nephrolithiasis is further increased by a high urine pH level and hypocitraturia, which is caused by proximal citrate reabsorption that is induced by acidosis.

- **The urine pH is abnormally elevated** despite systemic acidosis. Urine NH₄⁺ excretion is low.

  - There may be impairment of proton secretion in the distal nephron to a degree beyond that expected for the patient’s renal function.
  - Incomplete dRTA 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 dRTA

The hallmark of RTA is non-anion gap metabolic acidosis (NAGMA) or hyperchloremic metabolic acidosis. Important laboratory findings in dRTA are low serum HCO₃⁻, hyperchloremia, hypokalemia (except in hyperkalemic-type dRTA), hypercalciumia, hypocitraturia, and low urinary NH₄⁺. Serum calcium, serum phosphate, and urinary phosphate levels are normal.

Measurement of urinary NH₄⁺ by formaldehyde titration should be performed. Measurement of urinary Na⁺ is important, because low urinary sodium is associated with a voltage-dependent acidification defect. This measurement method is cumbersome; therefore, the urinary anion gap is calculated as an indirect method to approximate urinary NH₄⁺ excretion.
1. The urine anion gap (UAG) measurement is helpful to differentiate between renal and non-renal causes of NAGMA.

\[ \text{UAG} = [\text{Na}^+]_{\text{Ur}} + [\text{K}^+]_{\text{Ur}} - [\text{Cl}^-]_{\text{Ur}} \]

- The UAG is positive in normal conditions and in RTA. When urinary excretion of NH\(_4^+\) is high (as in extrarenal bicarbonate loss), the UAG becomes negative.
- Interpretation of the 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 the significant excretion of bicarbonate in the urine).

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

\[ \text{UOG} = [\text{Osm}]_{\text{Ur}} - (2[\text{Na}^+]_{\text{Ur}} + 2[\text{K}^+]_{\text{Ur}} + [\text{Urea}]_{\text{Ur}} + [\text{Glu}]_{\text{Ur}}) \]

- When there is an increased secretion of NH\(_4^+\), the UOG equals or is greater than 100 mmol/L, the value of the UOG/2 is roughly equal to [NH\(_4^+\)]_{\text{Ur}}. However, the UOG is invalid in conditions associated with a significant presence of unmeasured osmolals such as lithium.
- A urine pH level that is more than 5.5 suggests a renal acidification defect when the pH is measured in a fresh, early morning urine sample. Remember that type II RTA and type IV RTA can present with a urine pH level of < 5.5.

1. The ammonium chloride loading test is the most commonly used acid-loading test, in which 0.1 g/kg NH\(_4\)Cl is given orally to induce systemic acidosis and ABG and urine pH levels are monitored hourly. Normally, the urine pH should fall below 5.5 in the presence of systemic acidosis. A urine pH level that is 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. It is contraindicated in chronic liver disease, so calcium chloride is used to induce acidosis.

1. The sodium bicarbonate loading test is performed by oral or intravenous administration of sodium bicarbonate to alkalinize the urine (urine pH > 7.5). Normally, in the presence of steady-state serum bicarbonate (23–25 mEq/L) and alkaline urine, the urine CO\(_2\) is more than 70 mm Hg, the urine-to-blood pCO\(_2\) gradient (U-B pCO\(_2\)) is more than 20 mm Hg, and the fractional excretion of bicarbonate (FEHCO\(_3\)) is less than 5%.

\[ \text{FEHCO}_3(\%) = (\text{urine bicarbonate} \times \text{plasma creatinine}) / (\text{plasma bicarbonate} \times \text{urine creatinine}) \times 100 \]

In classic dRTA, the urine pCO\(_2\) is less than 50 mm Hg, the U-B pCO\(_2\) is less than 10 mm Hg, and the FEHCO\(_3\) is less than 5% on the sodium bicarbonate test. In voltage defect dRTA, the urine pCO\(_2\) is more than 70 mm Hg, the U-B pCO\(_2\) is more than 20 mm Hg, and the FEHCO\(_3\) varies from 5–10%.

Differential Diagnoses of dRTA

- 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 level may be helpful in preventing the formation of kidney stones.

**Therapy of dRTA**

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 a normal serum bicarbonate level (22–24 mEq/L).

Simple alkali replacement (1–3 mmol/kg per day 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:

\[
\text{required dose} = \text{desired change in serum bicarbonate} \times \text{body weight (kg)} \times 0.6
\]

In patients with a serum bicarbonate level 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. Secretion of growth hormone peaks during sleep, so 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. There is an inverse relationship between plasma HCO$_3^-$ and urinary calcium, so 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 dRTA**

**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 lead to renal failure. A woman with dRTA may also experience adverse pregnancy-related outcomes. Alternation in acid–base homeostasis occurs during a normal pregnancy; however, severe dRTA in pregnant women causes UTI or renal failure.

References


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