Renal Tubular Acidosis Type 4: Absolute Hypoaldosteronism (Aldosterone Insensitivity) in Children

Renal tubular acidosis (RTA) type 4, also called hyperkalemic renal tubular acidosis, is characterized by hyperchloremic metabolic acidosis, hyperkalemia, and decreased urinary NH$_4^+$ excretion, usually due to hypoaldosteronism or aldosterone resistance. Children usually present with growth failure or symptoms of an underlying condition. Treatment of hyperkalemia and alkali supplementation for the correction of acidosis are the mainstay of treatment. In this article, the etiology, pathophysiology, symptoms, diagnosis, differential diagnosis, treatment and prognosis of renal tubular acidosis type 4 are described.

Definition

Hyperkalemic RTA, also called RTA type 4, is characterized by defective regeneration of HCO$_3^-$, which results from decreased urinary NH$_4^+$ excretion, which is usually due to aldosterone deficiency or aldosterone resistance along with hyperkalemia.

Epidemiology of Absolute Hypoaldosteronism

The exact prevalence of RTA type 4 is unknown.
Etiology of Absolute Hypoaldosteronism

Primary

- Sporadic
- Genetic
  - **Congenital adrenal hyperplasia** (21-β-hydroxylase deficiency, 3-β-hydroxysteroid dehydrogenase deficiency, desmolase deficiency)
  - Primary Addison disease
  - **Hypoaldosteronism**
    - Pseudohypoaldosteronism (type 1- autosomal dominant or autosomal recessive, type 2-autosomal dominant)

Secondary

- Urologic cause – obstructive uropathy
- Intrinsic renal causes
  - Interstitial nephritis
  - Pyelonephritis
  - Chronic allograft rejection
  - Medullary cystic kidney disease
- Systemic causes
  - Diabetes mellitus (diabetic nephropathy)
  - Sickle cell nephropathy
  - Lupus nephropathy
  - Amyloidosis
- Adrenal insufficiency
  - Autoimmune adrenalitis
  - Infectious adrenalitis (human immunodeficiency virus infection)
  - Adrenal hemorrhage, adrenal carcinoma, bilateral adrenalectomy
- Drugs
  - Potassium-sparing diuretics – spironolactone, eplerenone, amiloride, triamterene
  - Antibiotics: trimethoprim, pentamidine
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Calcineurin inhibitors – cyclosporine, tacrolimus
  - Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin receptor blockers (ARBs)
  - Heparin and low-molecular-weight heparins

Epidemiology

Usually seen in middle to old age, but can also be seen in younger patients with underlying type 1 diabetes mellitus and sickle cell anemia.

Pathophysiology of Absolute Hypoaldosteronism

Collecting ducts in the kidneys play an important role in the regulation of acid-base balance. Secretion of H⁺ by H⁺-ATPase is modulated by **epithelial sodium channels (ENaC)** in principal cells. **Aldosterone** stimulates ENaC and H⁺-ATPase, thus stimulating secretion of H⁺ in collecting ducts. Aldosterone also increases reabsorption of Na⁺ and
increases luminal secretion of $K^+$ by creating negative intratubular potential and by inducing $Na^+/K^+$-ATPase.

Hyperkalemia decreases $NH_4^+$ excretion by two mechanisms: a) entry of $K^+$ into proximal tubular cells in exchange for $Na^+$ and $H^+$ induces intracellular alkalosis, which inhibits synthesis of ammonia; and b) $K^+$ competes with $NH_4^+$ for reabsorption by $Na^+/K^+/2Cl^-$ cotransporter in thick ascending limb of the loop of Henle, thus decreases medullary absorption of $NH_4^+$.

Aldosterone plays a key role in $K^+$ homeostasis and $H^+$ secretion and thus in the generation of $NH_3$. Hence, conditions that are associated with aldosterone deficiency (pseudohypoaldosteronism) or decreased renal responsiveness to aldosterone (pseudohypoaldosteronism) can cause RTA type 4. Lack of action of aldosterone leads to a failure of the secretion of $H^+$ and $K^+$ in collecting ducts, resulting in acidosis and hyperkalemia; ammoniagenesis is also decreased. Low $NH_4^+$ also contributes to impaired distal acidification.

In the state of aldosterone deficiency/resistance, the kidneys are able to establish a maximal $H^+$ gradient and thus are able to reduce urinary pH to less than 5.5.

As aldosterone is part of renin-angiotensin-aldosterone (RAA) axis, several renal disorders associated with hyporeninism are associated with hypoaldosteronism, and therefore with RTA type 4. However, conditions associated with aldosterone resistance (e.g., pseudohypoaldosteronism type 1) are associated with hyperreninism.

Spironolactone and eplerenone inhibit aldosterone action by competing for its receptors, while amiloride inhibits the action of aldosterone by inhibiting ENaC. NSAIDs inhibit renin secretion and impair angiotensin-II-induced aldosterone release. Calcineurin inhibitors induce aldosterone resistance, while ACE inhibitors/ARBs reduce aldosterone synthesis. Heparin and LMW heparins inhibit the release of aldosterone from zona glomerulosa of the adrenal cortex. Drugs like trimethoprim, pentamidine, etc cause hyperkalemia by inhibiting ENaC.

In pseudohypoaldosteronism type 1, there is loss-of-function mutation of MRL gene – aldosterone receptor gene; while pseudohypoaldosteronism type 2 (Gordon’s syndrome) results from mutations in WNK serine-threonine kinase genes.

Symptoms of Absolute Hypoaldosteronism

Usually asymptomatic unless accompanied by severe hyperkalemia.

Patients with RTA type 4 can present with growth failure during childhood. Polyuria is common and dehydration may be present due to salt wasting.

Life-threatening hyperkalemia is a rare presentation, except in pseudohypoaldosteronism type 1. Arterial hypertension is common in pseudohypoaldosteronism 2.

Clinical features of the underlying condition may be presenting symptoms. For example, children with obstructive uropathy may present with symptoms of acute pyelonephritis (fever, vomiting, foul-smelling urine, etc).
Diagnosis of Absolute Hypoaldosteronism

A hallmark of RTA type 4 is non-anion gap metabolic acidosis (NAGMA) or hyperchloremic metabolic acidosis and hyperkalemia. Important laboratory findings in RTA type 4 are low serum HCO$_3^-$ and hyperkalemia. Urinary excretion of citrate and phosphate is normal, while that of calcium may be normal or decreased. (High-yield information.)

Due to low urinary NH$_4^+$, Urine anion gap (UAG) is positive. Urinary osmolar gap (UOG) also helps to estimate urinary NH$_4^+$ excretion. Urine may be acidic or alkaline, but Urine pH is less than 5.3—5.5 in after performing acid loading with ammonium chloride loading test.

On performing a Sodium bicarbonate loading test, urine-blood PCO$_2$ gradient (U-B PCO$_2$) is more than 20 mm Hg, and fractional excretion of bicarbonate (FEHCO$_3$) is more than 5—10% in RTA type 4.

Transtubular potassium gradient (TTKG) helps to estimate the action of aldosterone on cortical collecting tubules. It is calculated as follows:

\[
TTKG = ([K^+]_{ur} \times [Osm]_{pl}) / ([K^+]_{pl} \times [Osm]_{ur})
\]

The normal value of TTKG is more than 4. If renal mechanisms are normal, the value of TTKG can be less than 2 in the presence of hypokalemia and more than 10 in the presence of hyperkalemia. If TTKG is less than 8 in the presence of hyperkalemia, hypoaldosteronism, aldosterone resistance, or impaired distal K$^+$ secretion should be suspected.

Low urine potassium: Creatinine ratio also suggests low urinary excretion of potassium.

Random serum renin and aldosterone levels are useful to diagnose hypoaldosteronism, with or without hyporeninism or hyperreninism. Remember that pseudohypoaldosteronism type 1 is characterized by elevated plasma renin and aldosterone levels, while pseudohypoaldosteronism type 2 is characterized by decreased plasma renin levels. (High-yield information.)

Imaging of the urinary tract may be helpful as obstructive nephropathy is an important cause of RTA type 4.

Unlike RTA type 1, there is no nephrolithiasis or nephrocalcinosis; unlike RTA type 2, there are no other tubular defects. Bone disease is not present in RTA type 4.

Differential Diagnoses of Absolute Hypoaldosteronism

- Other types of RTA
- Other causes of NAGMA
- Other causes of hyperkalemia

Therapy of Absolute Hypoaldosteronism

Normalization of serum potassium levels is an important goal in the management of RTA type 4 as it reduces acidosis by increasing urinary NH$_4^+$ excretion and by enhancing HCO$_3^-$
generation in proximal tubules. If correction of hyperkalemia does not improve acidosis, alkali supplementation is required to treat acidosis. Usually, alkali supplementation in a dose of 1.5—2 mEq/kg/day is sufficient in RTA type 4.

Loop diuretics alone or in the combination of a thiazide diuretic is helpful to increase potassium excretion. Potassium should be restricted in the diet and oral potassium binders (kayexalate) may be used to reduce potassium absorption from the intestines.

The cause must be treated, if possible. Congenital adrenal hyperplasia is treated with replacement therapy with fludrocortisone in a dose of 0.1—0.3 mg/day (0.05—0.15 mg/m²/day).

Complications of Absolute Hypoaldosteronism

- Complications include:
  - Permanent renal dysfunction.
  - Heart diseases-cardiac arrhythmias, dyspnea, due to hyperkalemia.
  - Muscular weakness.
  - Diabetes mellitus resulting from integrated hormonal disturbance.
  - Neurological manifestations like seizures, unconsciousness.

Prognosis of RTA type 4 depends upon the underlying condition.

Comparison of RTA type 1, type 2, and type 4 (High-yield information)

<table>
<thead>
<tr>
<th></th>
<th>RTA type 1 (Distal RTA)</th>
<th>RTA type 2 (Proximal RTA)</th>
<th>RTA type 4 (Hyperkalemic RTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important defect</strong></td>
<td>H⁺ secretion</td>
<td>HCO₃⁻ reabsorption</td>
<td>Aldosterone synthesis/effect</td>
</tr>
<tr>
<td><strong>Location of defect</strong></td>
<td>Distal tubule</td>
<td>Proximal tubule</td>
<td>Distal tubule</td>
</tr>
<tr>
<td><strong>Urine pH</strong></td>
<td>&gt; 5.5</td>
<td>&lt; 5.5</td>
<td>&lt; 5.5</td>
</tr>
<tr>
<td><strong>Serum Cl⁻</strong></td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Serum K⁺</strong></td>
<td>Low or Normal (high in hyperkalemic type)</td>
<td>Low or normal</td>
<td>High</td>
</tr>
<tr>
<td><strong>Urine ammonium</strong></td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Urine anion gap (UAG)</strong></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Urine calcium</strong></td>
<td>High</td>
<td>Normal or high</td>
<td>Normal or low</td>
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<tr>
<td><strong>Urine phosphate</strong></td>
<td>Normal</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Urine citrate</strong></td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td><strong>Urine PCO₂</strong></td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Urine-blood PCO₂</strong></td>
<td>Low (&lt; 20 mm Hg)</td>
<td>Normal (&gt; 20 mm Hg)</td>
<td>Normal (&gt; 20 mm Hg)</td>
</tr>
<tr>
<td><strong>Fractional excretion of HCO₃⁻ (FEHCO3)</strong></td>
<td>Normal (&lt; 5 %)</td>
<td>High (&gt; 10—15 %)</td>
<td>High (&gt; 5—10 %)</td>
</tr>
<tr>
<td><strong>Presence of other tubular defects</strong></td>
<td>Absent</td>
<td>Often present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Nephrolithiasis</strong></td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Bone disease</strong></td>
<td>Rare</td>
<td>Often present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Common causes

| Primary, autoimmune, sickle cell disease, lithium toxicity | Genetic forms, Fanconi syndrome, heavy metal toxicity | Congenital adrenal hyperplasia, obstructive nephropathy, drugs (spironolactone, NSAIDs) |

Review Questions

The answers can be found below the references.

1. **Which of the following is an important characteristic of RTA type 4?**
   
   A. Hypercalciuria  
   B. Positive urinary anion gap  
   C. Transtubular potassium gradient (TTKG) > 12  
   D. Fractional excretion of HCO3- (FEHCO3) < 5%  
   E. Urine-blood PCO2 < 20 mm Hg

2. **Which of the following drugs causes hyperkalemia by inhibiting epithelial sodium channels (ENaC)?**
   
   A. Amiloride  
   B. Cyclosporine  
   C. Heparin  
   D. Spironolactone

3. **Which of the following conditions are associated with RTA type 4 and is characterized by hyperreninism?**
   
   A. Diabetic nephropathy  
   B. NSAID-induced nephropathy  
   C. Interstitial nephritis  
   D. Pseudohypoaldosteronism type 1  
   E. Pseudohypoaldosteronism type 2

References


**Correct answers:** 1B; 2A; 3D

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