Pseudo-Renal Tubular Acidosis: Conditions Mimicking Renal Tubular Acidosis

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Hyperchloremic metabolic acidosis, particularly renal tubular acidosis, can pose diagnostic challenges. The laboratory phenotype of a low total carbon dioxide content, normal anion gap, and hyperchloremia may be misconstrued as hypobicarbonatemia from renal tubular acidosis. Several disorders can mimic renal tubular acidosis, and these must be appropriately diagnosed to prevent inadvertent and inappropriate application of alkali therapy. Key physiologic principles and limitations in the assessment of renal acid handling that can pose diagnostic challenges are enumerated.

Key Words: Hyperchloremic metabolic acidosis, Renal tubular acidosis, Pseudo-RTA, Respiratory alkalosis, Urine anion gap

INTRODUCTION

Renal tubular acidosis (RTA) encompasses a spectrum of disorders caused by the inability of the kidneys to conserve bicarbonate or adequately excrete an acid load. In the evaluation of low serum bicarbonate and normal anion gap, RTA is within the spectrum of differential diagnoses considered.[1] Aside from selective population-based studies, RTA has a low prevalence in the adult population.[2,3] Nevertheless, RTA is a diagnosis frequently considered by trainees who are often perplexed by the diagnostic challenges. Interestingly, in 1992, the pediatric neurologist Donald Lewis postulated that the child-protagonist Tiny Tim of the 1843 Dickens' classic, *A Christmas Carol*, had type 1 or distal renal tubular acidosis (dRTA). Lewis arrived at his vatic conclusion based on Tim's symptomatology and available therapeutics at that time, which included "alkali."[4] Although understanding of the pathophysiology of RTAs has considerably advanced, the diagnosis of RTA still requires a meticulous and algorithmic assessment of clinical, laboratory, and urinary parameters. Additional complexity may be encountered by the multiple, validated approaches that are available.[1,5,6]

RTA is classically categorized into type 1, 2, and 4. Proximal RTA (type 2) can be congenital or acquired, resulting in proximal tubular injury/dysfunction and subsequent bicarbonaturia. Proximal RTA is frequently associated with Fanconi syndrome, and this disorder usually becomes apparent by the variable presence of glycosuria, aminoaciduria, calciuria, uricosuria, phosphaturia, and low-molecular-weight proteinuria.[7] In contrast, dRTA typically presents without overt clues and requires a systematic approach for successful diagnosis. The omission of vital diagnostic steps can mislead to an erroneous diagnosis of dRTA. The hallmark of dRTA is the presence of hyperchloremic metabolic acidosis (HCMA) and limited urinary net acid excretion.[5] Classic features include a urine pH greater than 6, renal potassium wasting, and diminished urine net acid excretion, which is manifested by a "positive" urine anion gap (UAG). The evaluation of RTA should be established during steady state conditions, when patients are in the outpatient setting. Pseudo-RTA is often a (mis)diagnosis made in the inpatient setting when diagnostic principles are misapplied. Using clinical scenarios, we aim to illustrate clinical mimics of dRTA for which treatment by alkali would be erroneous.

PATIENT SCENARIO 1

An 80-year-old female with a history of degenerative joint disease presented to the emergency room with altered mental status. She was afebrile, and her heart rate was 80 beats per minute, respiratory rate was 28 breaths per minute, and blood pressure was 112/70 mm Hg. Her admission laboratory examination revealed the following serum values: sodium (Na^+) 139 meq/L, potassium (K^+) 3.5 meq/L, chloride (Cl^-) 118 meq/L, total carbon dioxide (tCO_2) 12 meq/L, blood urea nitrogen 12 mg/dL, and creatinine 1.02 mg/dL.

Hypobicarbonatemia

Close attention to history and physical examination findings is likely to yield a diagnosis in most acid-base disturbances. The hyperventilation is a vital clue in assessing the acid-base disorder of this individual, in which hypobicarbonatemia and hypocapnia are the predominant features. Low serum bicarbonate may be the consequence of metabolic acidosis (increased anion or normal anion gap) with loss or titration of bicarbonate or a renal adaptive response to respiratory alkalosis.[8] An arterial blood gas establishes the diagnosis of respiratory alkalosis, negating the possibility of the misdiagnosis of hypobicarbonatemia attributable to a HCMA. The arterial blood gas of the patient showed a pH 7.70, PCO_2 10 mm Hg, and calculated bicarbonate 12 meq/L. Further workup revealed an elevated salicylate level of 63 mg/dL, thereby establishing the diagnosis of salicylism. Renal mitigation of the alkalinizing effect of the depressed PCO_2 demands a decrement of serum bicarbonate, the extent to which it is predictable, depending on whether the duration of hypocapnia is acute

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(<48 hours) or chronic (>48 hours). Because the pH of the patient is extreme, validation of the blood gas is recommended, and the following equation, a modification of the Henderson-Hasselbalch equation, can accomplish this task.[8]

$$pH = 7.62 - LOG_{10}\left(\frac{PCO_2}{[HCO_3^-]}\right)$$

After rearrangement and applying rules of logarithms, the equation is used to solve for bicarbonate, given the 2 most precise terms of the blood gas, which are the pH and PCO_2. The solution of the equation yields a bicarbonate value that closely approximates to that of the reported value. Accordingly,

$$[HCO_3^-] = \frac{PCO_2}{10^{(7.62-pH)}} = \frac{10}{10^{(7.62-7.70)}} = 12 \text{ meq/L}$$

The initial temporizing response occurs within minutes and is mediated through tissue and blood buffers. Hemoglobin and plasma proteins account for approximately one-third of this compensatory response. An additional contribution to buffering proceeds via tissue release of protons. Overall, the decline in bicarbonate concentration is a proportional response to the decrement in PCO_2.[9] We refer to the clinical scenario of pure, acute respiratory alkalosis with hypobicarbonatemia misdiagnosed as an RTA or as a pseudo-pseudo-RTA because acidemia and RTA are both absent. As demonstrated, pseudo-RTA is determined by blood gas analysis. Sustained hypocapnia, as occurred in this patient, fosters additional adaptive responses, the basis of which can lead to a mimicking of dRTA as detailed in the following clinical vignette.

CLINICAL SUMMARY

- Pseudo-renal tubular acidosis (pseudo-RTA) is a heterogeneous group of disorders characterized by hyperchloremia, hypobicarbonatemia, and metabolic acidosis that is not due to intrinsic renal tubular dysfunction.
- Diagnosis of RTA requires a structured approach in assessing primary and secondary acid-base responses.
- Respiratory alkalosis can present with a picture that is similar to distal RTA; blood gas analysis is mandatory.
- A fundamental appreciation of the limitations and application of urinary indices is required to evaluate metabolic acidosis

PATIENT SCENARIO 2

A 55-year-old female with a history of cerebrovascular injury with residual hemiparesis, alcohol-induced cirrhosis, and hypertension presented with altered mental status. The vital signs were temperature 38.5°C, pulse 110 beats per minute, respiratory rate 18 breaths per minute, and blood pressure 80/58 mm Hg. Hemodynamic parameters improved after administration of intravenous saline. The initial laboratory examination showed the following: Na^+, 128 meq/L; K^+, 3.5 meq/L; Cl^-, 99 meq/L; tCO_2, 19 meq/L; blood urea nitrogen, 22 mg/dL; creatinine, 1.42 mg/dL; and albumin 3 g/dL. Prior laboratory data were not available for comparison. An arterial blood gas analysis, obtained to evaluate altered mental status, showed a pH 7.40, PCO_2 33.3 mmHg, and bicarbonate 20.1 meq/L. The urine dipstick pH was 6.0. Urine chemistries were Na^+ 12 meq/L, K^+ 62 meq/L, and Cl^- 22 meq/L.

In contrast to the first clinical scenario, hyperventilation is not an obvious feature that leads one to immediately suspect respiratory alkalosis. Furthermore, important elements of the history and physical examination may be difficult to ascertain during the initial encounter. In this patient, the systemic pH within the normal range can be explained by either chronic respiratory alkalosis or a mixed disorder (respiratory alkalosis and metabolic acidosis).

When the clinical history supports chronic respiratory alkalosis, determining whether the decrease in bicarbonate is appropriately compensated is critical to complete analysis of the blood gas. Metabolic compensation during chronic respiratory alkalosis was investigated during hypobaric hypoxia by Krapff and associates in their seminal study in humans; a decrease of 10 mm Hg of PCO_2 was paralleled by a decrease in bicarbonate of 0.4 to 0.5 meq/L.[10] Computing the expected serum bicarbonate for a PCO_2 of 33 mmHg in our patient closely approximates the expected compensation, signifying the presence of chronic respiratory alkalosis.

If respiratory alkalosis is not the initial consideration and one presumes metabolic acidosis to be the primary disorder, assessment of urinary ammonium (NH_4^+) handling can be pursued to identify the origin of hyperchloremic acidosis, ie, renal or nonrenal. In many diagnostic algorithms of normal anion gap acidosis, the evaluation of the urine anion gap is recommended as the next step.[1,11] The UAG representing the difference between the principal cations (Na^+ and K^+) and anions (Cl^-) is used to reflect renal ammonium excretion. A negative value denotes excretion of unmeasured cations (UCs) (NH_4^+) with Cl^-. A positive UAG implies decreased urinary NH_4^+ excretion as encountered with dRTA.[12,13] In our patient, the urine pH of 6, positive UAG of 52 meq/L, and K^+ in the low normal range point toward a diagnosis of dRTA. Examining the physiologic response and limitations of the aforementioned diagnostic tests (Table 1) delineates the mechanisms whereby respiratory alkalosis mimics dRTA.

Respiratory Alkalosis and Renal Compensation

Bicarbonaturia may be detected within 2 to 5 hours of the onset of acute respiratory alkalosis.[8,14,15] A net decrease in luminal activity of the Na^+-H^+ exchanger and basolateral Na^+/HCO_3^- exchanger subsequently occurs.[16] Experimental dog studies, later replicated in 8 acutely hyperventilating males, documented that a 10 mm Hg decrease in PCO_2 was accompanied by a serum bicarbonate decrement of 2 meq/L. [1,15] Persistent hypocapnia elicited