Oman Medical Journal (2011) Vol. 26, No. 4: 271-274
DOI 10. 5001/omj.2011.66

Distal Renal Tubular Acidosis, Hypokalemic Paralysis, Nephrocalcinosis, Primary Hypothyroidism, Growth Retardation, Osteomalacia and Osteoporosis Leading to Pathological Fracture: A Case Report

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Received: 06 May 2011 / Accepted: 07 Jul 2011

Abstract

Renal tubular acidosis (RTA) is a constellation of syndromes arising from different derangements of tubular acid transport. Recent advances in the biology of urinary acidification have allowed us to discern various molecular mechanisms responsible for these syndromes. RTA often presents as renal stone disease with nephrocalcinosis, ricket/osteomalacia and growth retardation in children with ultimate short stature in adulthood. The case reported here has features of distal renal tubular acidosis (dRTA), hypokalemic paralysis, primary hypothyroidism, growth retardation, osteomalacia and osteopenia leading to stress fracture. All these features presenting in a single case (as in our case) is a rare occurrence, so far other cases of distal renal tubular acidosis (dRTA) have been reported.

Keywords: Osteoporosis; Metabolic acidosis; Hypokalemic paralysis.

Introduction

Renal tubular acidosis (RTA) is non-uremic defects of urinary acidification. Renal tubular acidosis is characterized by a normal anion gap hyperchloremic metabolic acidosis; plasma potassium may be normal, low or high-depending on the type of RTA. These syndromes differ from uremic acidosis which is associated with a high anion gap, decreased glomerular filtration with enhanced proton secretion by each remaining nephron.

In 1946, Albright et al. described dRTA as a distinct entity.[1] The clinical syndrome described, consists of hypokalemia, hyperchloremic metabolic acidosis, inability to lower urine pH below 5.5 in the face of systemic acidosis, nephrocalcinosis and nephrolithiasis. Additional features included osteoporosis/osteomalacia, autoimmune primary hypothyroidism and stunted growth with normal puberty in our patient. The syndrome was designated "distal renal tubular acidosis," since the establishment of a large pH gradient between urine and blood is a function of the distal nephron.

The physician should be familiar with the clinical presentation, and the correct management of the illness, in order to prevent or ameliorate nephrocalcinosis, rickets/osteomalacia or growth failure.

Case Report

A 23-year-old girl presented to the emergency department (ED) with history of progressively worsening, generalized muscle weakness, inability to walk without support for four days. She denied having any fever, chronic diarrhea, headache, abdominal pain, paresthesias, sensorineural deafness or any other drug intake. She was known to have dRTA since at the age of 14 years old. She had a history of recurrent admissions with hypokalemic paralysis since her diagnosis of dRTA. The patient had a history of pathological fracture of the shaft of right femur and tibia three years earlier; diagnosed and managed by our orthopedic team conservatively. All of (recurrent hypokalemia and fracture) these had been happening due to her poor drug compliance. She is a known hypothyroid for about 1 year and was on replacement therapy. Her menstrual period was regular. No family members were affected with similar illness.

On physical examination, she was afebrile. Her pulse was regular with a rate of 72/min. Her blood pressure was 120/60 mm Hg, and had a respiratory rate of 18 breaths/min. The thyroid gland was of normal size. She appeared uncomfortable and generally fatigued, but was alert and oriented. Her lungs were clear to auscultation. The heart rhythm was regular and was without murmur, rub or gallop. Her abdomen was nontender without masses. The extremities were without edema and the radial pulses were strong bilaterally. Neurologic examination revealed muscle power of 4/5 in upper and 2/5 in lower extremities. Cranial nerves II-XII were normal and symmetric. She had negative Babinski and Hoffmann signs. Her height was 145 cm which is (>2.5 standard deviation) below the mean and her weight was 40 kg.

An electrocardiogram (ECG), urine analysis and basic metabolic panel were completed soon after arrival in ED. Her ECG was normal. Initial laboratory testing revealed normal complete

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blood count, serum glucose of 98 mg/dL, sodium of 140 mEq/L (normal range: 135-145 mEq/L), potassium of 2.7 mEq/L (normal range: 3.6-5.0 mEq/L), chloride of 116 mEq/L (normal range: 98-109 mEq/L), bicarbonate of 10 mEq/L (10 mmol/L; normal range: 22-31 mEq/L), anion gap of 12 mEq/L (normal range: 6-16 mEq/L), blood urea nitrogen (BUN) of 12 mg/dL (normal range: 7-21 mg/dL), creatinine of 0.80 mg/dL (normal range: 0.6-1.2 mg/dL), calcium of 7.5 mg/dL (normal range: 8-12 mg/dl), phosphate of 1.8 mg/dL (normal range: 2.5-5 mg/dL), albumin of 3.9 g/dl (normal range: 3.8-5 g/dl) and alkaline phospatase of 350 U/L (normal range: 39-117 U/L).

These values were consistent with a non-anion gap hyperchloremic metabolic acidosis with associated hypokalemia and hypocalcemia. As a result of hyperchloremic metabolic acidosis, an arterial blood gas (ABG) was subsequently performed; this showed a pH of 7.20, a partial pressure of carbon dioxide (pCO_2) of 22 mm Hg, a partial pressure of oxygen (pO_2) of 100 mm Hg, and a bicarbonate (HCO_3) of 10 mEq/L (10 mmol/L). The urinary pH was 7.0, while PTH was 68 pg/ml (normal range: 7.0-65 pg/ml). Other hormonal profiles such as FT4, TSH, LH, FSH, prolactin and growth hormone (GH) were normal. Her antithyroid peroxidase level was 443 IU/ml (normal range: up to 35 IU/ml) and 25-OH cholecalciferol was 18 ng/ml (normal range: 20-100 ng/ml).

The ECG and chest radiograph were normal. Plain X-ray of the abdomen showed bilateral nephrocalcinosis. The renal ultrasound showed hyperechoic regions in the renal medulla consistent with bilateral nephrocalcinosis. Her bone mineral density by dual X-ray absorptometry (DXA) was -3, consistent with osteoporosis. She was managed with Eltroxin 100 mcg daily, oral sodium bicarbonate (325 mg) 3 tablets thrice daily, intravenous potassium chloride (KCL) infusion followed by oral KCL 600 mg thrice daily, oral Alfacalcidiol 0.5 mcg daily and calcium carbonate 500 mg twice daily. The patient completely recovered from muscle weakness and was discharged home on hospital day 7, and she had a normal basic metabolic panel during discharge. During her subsequent follow-up here (KSA) and in Kuwait, she was doing well.

Discussion

Distal RTA (RTA type I) is a rare renal disorder characterized by non-anion gap hyperchloremic acidosis and hypokalemia. In this condition, the alpha intercalated cells of the cortical collecting duct of the distal nephron fail to secrete acid into the urine. This failure of acid secretion leads to an inability to acidify the urine to a pH <5.5. Because renal excretion is the primary means of eliminating acid from the body, there is consequently a tendency towards systemic acidemia. This leads to the clinical features of RTA type I, which include: Normal anion gap hyperchloremic metabolic acidosis; Hypokalemia (from multiple mechanisms, but often severe during periods of stress); Nephrocalcinosis; Nephrolithiasis (related to an inability to acidify urine); Hypercalciuria, and low urinary citrate); Loss of calcium from bones (which can cause rickets in children and osteomalacia in adults).[2]

RTA type I is either inherited or acquired. Inherited RTA type I can be either autosomal-dominant or autosomal-recessive. Autosomal-recessive RTA type I often presents in infancy, whereas autosomal-dominant RTA type I may not present until adolescence or young adulthood.[3] Some patients with autosomal recessive distal RTA have associated sensorineural hearing loss.[4] Mutations in the genes encoding carbonic anhydrase (CA) II, kidney anion exchanger-1 (kAE1), and subunits of the H+-ATPase have been identified in patients with distal RTA.[5] Some genetic disorders, such as Ehler-Danlos syndrome, or Wilson's disease, have also been associated with RTA type I.[6] In the acquired form, the disorder can be caused by drugs, autoimmune diseases, or by infection.[6] Some of the more common acquired forms are caused by Sjögren syndrome, lupus, hepatitis, treatment with amphotericin B, toluene toxicity, and chronic pyelonephritis.[7,8]

The clinical manifestations of RTA type I depend upon the disease type, severity and whether it is acquired or inherited. The inherited form of RTA type I causes similar metabolic abnormalities, but it is more likely to result in decreased bone mineralization and growth retardation.[9] Both forms, however, have hypokalemia, which results in muscle soreness, flaccid paralysis, and electrical cardiac disturbances. The most common cause of death related to RTA type I is hypokalemia-induced cardiac dysrhythmia.

The second type of RTA is proximal renal tubular acidosis (RTA type II), which is caused by an inability to reabsorb bicarbonate in the proximal tubules. RTA type II may occur secondary to generalized dysfunction of the proximal tubules and can be associated with increased urinary excretion of glucose, uric acid, phosphate, amino acids, and protein.[10] The disorder most often occurs in the context of Fanconi syndrome, light chain nephropathy, multiple myeloma, or drug exposures.[10] Since the clinical features of both RTA type I and RTA type II can be similar, distinguishing between them can be a diagnostic challenge. These two causes of nonanion gap acidosis with hypokalemia can be distinguished relatively easily, with some laboratory testing. The easiest and most readily tested laboratory examination is the urine pH. In RTA I, the distal tubule is unable to acidify the urine and results in a urine pH that is above 5.5. RTA type II, however, has intact distal acidification which, together with an ability of the proximal tubule to reabsorb filtered bicarbonate once its concentration has fallen below its abnormally low tubular reabsorptive capacity, results in a urine pH <5.5. With these mechanisms, RTA II usually does not cause as profound a serum acidosis as RTA I. For example, it is not uncommon to have serum bicarbonate of less than 10 mEq/L (10 mmol/L) with RTA type I, whereas in RTA type II the bicarbonate is usually greater than 15 mEq/L (15 mmol/L).

Type III RTA is the rarest of the four forms and it is basically a combination of both type I and type II RTA. Type III RTA is usually the result of an inherited carbonic anhydrase II mutation, and it gives rise to an autosomal-recessive syndrome of metabolic acidosis, hypokalemia, osteoporosis, cerebral calcification, and mental retardation.

RTA type IV, also called hyperkalemic RTA, is caused by either aldosterone deficiency or resistance of the renal tubule to the actions of aldosterone. This form is readily distinguished from RTA types I and II because RTA type IV results in hyperkalemia rather than hypokalemia.

The earlier data of Brenner et al. indicated that type I RTA occurred more frequently in patients older than 18 years of age and had a female predominance.[11] Type II RTA occurred primarily in the pediatric group aged less than 18 years with a male predominance. Previously, type IV RTA was thought to be the second most common type of RTA. However, with increasing recognition of type IV RTA secondary to aldosterone resistance as in obstructive uropathy, or to aldosterone deficiency, and with more patients with obstructive uropathy from congenital posterior urethral valve or in elderly men with prostatic hypertrophy, type IV RTA is now widely regarded as the most common type of RTA.[12] The distinguishing features of the different RTAs are summarized in Table 1.[13]

Table 1: Distinguishing features of the different RTAs.

	RTA type I	RTA type II	RTA type IV
Primary defect	**Impaired ability to excrete H^+ in distal tubule**	**Impaired HCO_3**	**Decreased secretion of aldosterone or decreased effect**
Minimum urine pH	pH>5.5	pH<5.5	pH<5.5
Stones	Yes	No	No
Hyperchloremic acidosis	Yes	Yes	Yes
Serum potassium	Low-normal	Low-normal	High
Plasma Bicarbonate	<10 meq/L	12-20 meq/L	>17 meq/L

The diagnostic studies include serum electrolytes, ABG, urine analysis, a urinary PH, 24-hour urine citrate and calcium to diagnose RTA type I. In a patient with a borderline acidosis and hypokalemia, an acid load test can often be diagnostic. This test entails giving an acid load of 0.1 g/kg of ammonium chloride or fludrocortisone/furosemide and then checking the urine pH 4-6 hours later.[14] The test is considered positive (dRTA) if the urine pH remains above 5.5. The acid load test, however, is not advisable during periods of profound acidosis, and it should be used only among stable patients in otherwise non-diagnostic cases. An ECG should be done if there is suspicion for severe hypokalemia, which often presents as muscle weakness. Renal imaging can often show evidence of nephrolithiasis or nephrocalcinosis.

The cornerstone of medical treatment for RTA type I first entails addressing the underlying metabolic derangements. This is accomplished by replenishing potassium with intravenous and oral potassium chloride or potassium citrate. The latter is often more beneficial in patients with recurrent renal stones.[15] In addition, oral sodium bicarbonate (1-2 mEq/kg/day) can often help meet the alkali requirements and compensate for the lost bicarbonate. In inherited RTA type I, early medical therapy with alkali can mitigate growth retardation and bone demineralization. The use of oral alfacalcidiol 0.25-1 mcg per day is advocated if there is no satisfactory response with the parent vitamin D treatment. Additional treatment with phosphate is necessary in a dose of 1-3 g of elemental phosphorous per day, given in 4-5 divided doses.[16] Carefully monitoring of alkaline phosphatase, serum calcium and calciuria is necessary to prevent hypercalcemia in these patients.

The diagnosis of dRTA in our case was made on the basis of the patient's presentation of profound weakness (hypokalemic paralysis), non-anion gap hyperchloremic metabolic acidosis, associated with hypokalemia, hypocalcemia and nephrocalcinosis.

The arterial blood gas demonstrated a profound metabolic acidosis with a pH of 7.20, further confirming the diagnosis. It was possible to characterize the type of RTA by looking at the urine pH, which was 7.0 and nephrocalcinosis. This is consistent with renal tubular acidosis (RTA) type I, also known as dRTA. She had primary hypothyroidism and history of pathological fracture most likely due to osteoporosis related to chronic metabolic acidosis of dRTA. She had also nephrocalcinosis and growth retardation.

The mechanisms underlying hypokalemia in distal renal tubular acidosis have not been fully elucidated. The hypokalemia is particularly prevalent in the acquired forms. Hypokalemia probably results from increased kaliuresis due to renal tubular leakage, decreased proximal tubular reabsorption in the face of acidosis and hypocapnia, and aldosterone stimulation.[17]

It is important to differentiate from other causes of hypokalemia like familial periodic paralysis (FPP), thyrotoxicosis, hyperaldosteronism and gastrointestinal loss; because the treatment is different and bicarbonate therapy can deteriorate familial hypokalemic periodic paralysis; on the other hand it is the mainstay of therapy in RTA.

The concurrence of renal tubular acidosis and autoimmune thyroid disease has been reported before. Although the mechanism remains unclear, distal renal tubular acidosis has been well documented in the presence of a variety of autoimmune disorders including thyroid disease, Sjogrens syndrome and systemic lupus erythematosus. Symptoms of renal tubular acidosis usually resolve rapidly with substitution of thyroid hormone.[18]

However, autoimmune primary hypothyroidism in our patient was evidenced by the high titer of antithyroid peroxidase of 443 IU/ml (normal range: up to 35 IU/ml), which developed after the development of dRTA and did not resolve after thyroid hormone replacement, which implies of its non-association.

Bone is critically involved in buffering during the chronic stages of metabolic acidosis.[19,20] Chronic metabolic acidosis may trigger the release of alkali and calcium from the bone and eventually lead to reduction of bone mass and osteoporosis. Sanchez and Libman described both proximal and distal renal tubular acidosis in eight patients with osteoporosis.[21] Cases of distal RTA with bony deformities and multiple bone fractures have been reported in the literature.[22]

Our patient had severe osteoporosis as evidenced by BMD of -3 along with history of pathological fractures, secondary

hyperparathyroidism [PTH of 68 pg/ml (normal range: 7.0-65 pg/ml)] due to hypocalcemia and also have osteomalacia as explained by low level of calcium of 7.5 mg/dL (normal range: 8-12 mg/dl), phosphate of 1.8 mg/dL (normal range: 2.5-5 mg/dL) and 25-OH vitamin D of 18 ng/ml (normal range: 20-100 ng/ml) and high alkaline phospatase of 250 U/L (normal range: 39-117 U/L). Thus pathological fractures resulted from a combination of ostomalacia, osteoporosis, and secondary hyperparathyroidism due to long standing inadequately treated (poor compliance) dRTA.

Hypercalciuria, hyperphosphaturia, hypocitraturia and a high urinary pH are the main events that predispose RTA patients to develop renal stones.[23] Urinary citrate is an inhibitor of the crystal aggregation and precipitation. When citrate excretion is reduced, more calcium is chelated, thus aggravating urolithiasis and nephrocalcinosis.[24]

We did not monitor urinary calcium and phosphate level because in the presence of replacement therapy these elements are uninterpretable. Moreover, there are no facilities for performing urinary citrate level tests in our center. Thus we could not delineate the cause of bilateral nephrocalcinosis in this case appropriately.

The mechanism of growth failure in acidosis may be related to a dysfunction of the growth hormone/ insulin like growth factor (IGF) axis including the growth hormone receptor mRNA and IGF-I receptor mRNA.[25]

GH level was normal in our patient. The stunted growth in this case may be due to chronic acidosis itself and chronic acidosis induced loss of bone minerals and inadequate production of 1,25 dihydroxycholecalciferol as evidenced by low levels of 25-OH cholecalciferol at 18 ng/ml (normal range: 20-100 ng/ml).

There was a negative family history in our case; however a negative family history does not exclude autosomal dominant (AD) inheritance. Growth retardation is common in AD inheritance. Although we could not perform genetic analysis; the possibility of AD dominant inheritance in this case cannot be excluded.

Conclusion

It is important to differentiate RTA from FPP because during an acute attack administration of sodium bicarbonate in FPP would facilitate intracellular potassium flux and fatal hypokalemia may occur. In FPP oral potassium and acetazolamide are useful in preventing the attacks but acetazolamide is contraindicated in RTA as it produces acidosis. Recurrent hypokalemic paralysis with apparently progressive symptoms should be evaluated for an underlying disorder such as dRTA that could not only be potentially treatable but also achievable in growth velocity, adequate pubertal development and adult height near that of the normal parental height.

Acknowledgements

The author reported no conflict of interest and no funding was received for this work

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