Case Report

Distal Renal Tubular Acidosis in a Patient with Sjögren’s Syndrome: Case Report and Literature Review

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Abstract

Distal renal tubular acidosis (dRTA) is associated with inadequate urinary acidification by the distal nephron. dRTA can present as either an inherited or acquired condition such as autoimmune disorders. The reported prevalence of renal involvement in Sjögren’s syndrome (SS) patients varies widely, ranging from 2 to 67 percent. A defect in distal acidification occurs in up to 25 percent of patients with Sjögren’s syndrome. We report a 32-year-old woman who presented with progressive flaccid quadriparesis. Laboratory investigations showed severe hypokalemia with renal K+ wasting and hyperchloremic metabolic acidosis. A positive urine anion gap with alkaline urine and hypercalciuria with nephrolithiasis were consistent with the diagnosis of distal RTA. Further investigations revealed Sjögren’s syndrome as the underlying cause of distal RTA. (Acta Nephrologica 2011; 25: 201-204)

KEY WORDS: renal tubular acidosis (RTA), hyperchloremic metabolic acidosis, hypokalemia, Sjögren’s syndrome (SS)

Introduction

Renal tubular acidosis (RTA) refers to a syndrome with impaired reabsorption of the filtered bicarbonate and/or hydrogen ion (H+) excretion. The clinical entity results in a normal anion gap hyperchloremic metabolic acidosis with a relatively preserved glomerular filtration. Plasma potassium (K+) may be normal, low or high, depending on the type of RTA. There are four subgroups of RTA; among them, type 1 or distal and type 2 or proximal are the common ones. Both of them can present as either an inherited or acquired condition. Autoimmune disorders, such as Sjögren’s syndrome (SS), are found among the causes of dRTA. SS can occur alone or in association with rheumatoid arthritis, systemic lupus erythematosus, and occasionally scleroderma. We report a case of Sjögren’s syndrome with distal RTA.

Case Report

A 32-year-old woman was admitted due to progressive muscle weakness for 4 days. Myalgia was reported. She also had symptoms of dry mouth, dry eyes and arthritis at the time of admission. She had no significant major diseases but several episodes of mild hypokalemia, with serum K+ level ranging 3.1-3.3 mmol/L, were found in the last 4 years. Her family members had no similar history. She denied vomiting, diarrhea, the use of diuretics or other special medications. On admission, her blood pressure was 131/83 mmHg, pulse rate 94/min, respiratory rate 18/min and body temperature 37.2°C. Her consciousness was alert. Physical examination showed no enlargement of the parotid glands. Severe dental caries were noted. Muscle power of upper limbs was grade 4 and that of lower limbs was grade 3 with hyporeflexia but
The laboratory workup (Table 1) during admission showed severe hypokalemia, serum K⁺ 1.8 mmol/L while urine potassium level was 22.1 mmol/L and transtubular potassium concentration gradient (TTKG) was 9.9, indicating renal K⁺ wasting. Arterial blood gas analysis revealed pH 7.35, carbon dioxide (pCO₂) 20.3 mmHg, and bicarbonate (HCO₃⁻) 10.9 mmol/L. Urinalysis showed pH 7.5 with mild proteinuria (protein 1+) without glycosuria or casts. Plasma anion gap was 10.1 mmol/L and her urine anion gap was 20.3 mmol/L. Subsequent plasma aldosterone and renin activity were within normal limit. Hypercalcuiuria, 8.85 mmol/24 hours was found and serum intact parathyroid hormone level was not elevated, 16.5 ng/L. Bilateral renal calculi were seen by computed tomography (CT) of abdomen (Fig. 1). The presence of a normal anion gap hyperchloremic metabolic acidosis, alkaline urine with positive urinary anion gap, profound hypokalemia with high TTKG, hypercalcuiuria and nephrolithiasis were consistent with a diagnosis of distal RTA. Aggressive replacement therapy with intravenous KCl 120 mEq/day restored her muscle strength 24 hours later and then she received oral KCl 64 mEq/day. Provision of 15 mEq/day of potassium citrate also followed. To determine the causes of dRTA, rheumatology and immunology tests were done and showed positive anti-Ro and La antibodies, high antinuclear antibody and rheumatoid factor, normal C₃ and low C₄ level. The typical sicca syndrome was present and Shirmer’s test was positive. After the exclusion of secondary Sjögren’s syndrome by physical examination (no skin rash or taut skin, joint deformity), laboratory studies (normal liver enzymes, normal thyroid function) and immunologic test (negative anti-dsDNA), the diagnosis of primary SS was made. The patient was referred to a rheumatologist and treated with prednisolone (0.5 mg/kg per day) and hydroxychloroquine (200 mg twice daily). She was discharged with stable condition and followed up at the rheumatology clinic. Serum potassium and bicarbonate were tested regularly during routine follow-up and had been maintained within normal limits on 30 mEq of potassium citrate and 16 mEq of oral slow-release potassium chloride per day.

Table 1. Laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Serum Na (mmol/L)</td>
<td>138</td>
<td>136-145</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>1.8</td>
<td>3.5-5.1</td>
</tr>
<tr>
<td>Serum Ca (mmol/L)</td>
<td>2.5</td>
<td>2.2-2.6</td>
</tr>
<tr>
<td>Serum Cl (mmol/L)</td>
<td>117</td>
<td>98-107</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg water)</td>
<td>281</td>
<td>1.0-1.4</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.2</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>Mg (mmol/L)</td>
<td>5.2</td>
<td>3.4-7</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>10.9</td>
<td>22-28</td>
</tr>
<tr>
<td>pH</td>
<td>7.35</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>15</td>
<td>7-20</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.9</td>
<td>0.7-1.2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0</td>
<td>3.4-4.8</td>
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</tbody>
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Fig. 1. Abdominal CT showing bilateral renal calculi (white arrow).
**Discussion**

RTA was first described in infants with calcium infarction of the kidneys in 1935 (1), which was confirmed as a renal tubular disorder by Albright et al. in 1946 (2) and designated as “renal tubular acidosis” in 1951 (3). The renal acid-base homeostasis may be divided into two processes: reabsorption of filtered HCO$_3^-$, which occurs in the proximal convoluted tubule; and excretion of ammonium (NH$_4^+$), which takes place in the distal nephron. Among the four types of RTA, dRTA is caused by impaired distal acidification and has the inability to reduce urinary pH to below 5.5. Distal urinary acidification abnormalities may arise from transepithelial voltage defects, permeability defects, or proton secretory defects. The secretory or classic dRTA is due to two defective proton pumps, H$^+\text{-ATPase}$ and H$^+,K^+-\text{ATPase}$, located in the $\alpha$-type intercalated cells of the collecting duct (4). Metabolic acidosis results in decreased proximal sodium reabsorption, increased distal delivery of sodium and hence increased kaliuresis. Sodium wastage results in extracellular volume contraction and secondary hyperaldosteronism. Hypokalemia and potassium wasting may be in part a consequence of elevated levels of aldosterone commonly seen during acidosis. Amelioration of hypokalemia usually occurs after correction of the acidosis with bicarbonate therapy (5). In adults, dRTA frequently develops as a consequence of autoimmune disorder such as SS and systemic lupus erythematosus (6, 7).

The presence of proximal or distal RTA should be considered in any patient with an unexplained normal anion gap metabolic acidosis. Rapid distinction between proximal and distal RTA can be quickly performed by the study of the urine anion gap or osmolal gap. In patients with dRTA, the urine anion gap is positive or an osmolal gap below 100 mmol/L, because the defect in distal acidification results in low urine NH$_4^+$ levels (8). If the value of plasma K$^+$ is normal or decreased, the demonstration of an inability to reduce urine pH to below 5.5, either after NH$_4$Cl loading or after furosemide administration, establishes the diagnosis of distal RTA. This diagnosis is further supported by the finding of a low urine-to-blood PCO$_2$ gradient, less than 20 mmHg, after NaHCO$_3$ or neutral phosphate loading. In distal RTA, fractional excretion of HCO$_3^-$ at normal plasma HCO$_3^-$ concentration should not exceed 5% of the filtered load. When plasma K$^+$ is increased, the urine pH higher than 5.5 after NH$_4$Cl loading will permit the identification of a patient with hyperkalemic distal RTA caused by a “voltage dependent” defect (9). TTKG is employed to gauge renal potassium secretion by the cortical collecting duct, indirectly assessing mineralocorticoid bioactivity in patients who have hypo- or hyper-kalemic. TTKG values higher than 7 to 8 during hypokalemia in combination with a ratio of urine potassium (in mmol)/creatinine (in mmol) higher than 1.5 or higher than 15 mmol K$^+$/g creatinine, and 24-hour urinary potassium higher than 15 mEq per day point to renal loss due to increased distal K$^+$ secretion (10). An extrarenal cause of hypokalemia is suggested by a TTKG of less than 3. In our hypokalemic patient with kaliuresis, TTKG higher than 8 suggested renal potassium loss. Furthermore, metabolic acidosis suppresses proximal and distal calcium reabsorption by decreasing apical calcium entry. The clinical sequelae are hypercalcuria, nephrocalcinosis, and osteomalacia or renal rickets. The simultaneous reduction in urinary citrate levels during metabolic acidosis and the persistently alkaline urine enhance the development of nephrocalcinosis. Numerous investigators have noted an association between vitamin D deficiency and RTA. Metabolic acidosis suppresses 25-hydroxyvitamin D3-lc-hydroxylase system. Correction of the vitamin D deficiency has allowed correction of the proximal tubule dysfunction (11).

SS is a triad of dry eyes, dry mouth and arthritis with inflammation and destruction of exocrine glands, lacrimal glands and salivary glands, which was described by the Swedish ophthalmologist Henrik Sjögren in 1933 (12). American-European classification criteria, the gold standard for SS, proposed in 2002 consisted of six items (13). These are ocular symptoms of inadequate tear production, ocular signs of corneal damage due to inadequate tearing, oral symptoms of decreased saliva production, salivary gland histopathology demonstrating foci of lymphocytes infiltration, tests indicating impaired salivary gland function and presence of autoantibodies (anti-Ro/SSA and/or anti-La/SSB). Patients who have symptoms and findings that satisfy four or more of the American-European consensus criteria probably have SS. The diagnosis of SS was made in our patient on the basis of dry eyes, dry mouth, arthritis and autoantibodies. The reported prevalence of renal involvement in SS patients ranged from 2 to 67 percent (14). The most common lesion is distal renal tubular acidosis, tubulointerstitial disease presenting as Fanconi’s syndrome, or impairment of renal concentrating function (15). The proximal tubule dysfunction is quite uncommon in SS and there is no evidence for it in our patient. A defect in distal acidification occurs in up to 25 to 40 percent of patients with SS (16, 17). Several patients have been described in whom immunocytochemical analysis of tissue obtained by renal biopsy showed complete absence of the H$^+\text{-ATPase}$ pump in the $\alpha$-type intercalated cells in the collecting tubules that is largely responsible for distal proton secretion (18, 19). Another possible mechanism is the presence of high titers of an autoantibody directed against...
carbonic anhydrase II. Inhibition of this enzyme would result in the generation within the cell of fewer hydrogen ions available for secretion (20). The pathogenesis of dRTA in SS is specific immune-mediated tubulo-interstitial nephropathy, and glucocorticoid therapy results in improvement in the exocrine and extra-glandular involvement, as shown in our patient. SS typically affects middle-aged women; however, it could is sometimes discovered elderly men too (21).

Treatment for distal RTA aims to provide an adequate base for balancing $H^+$ production. A mixture of Na$^+$ and K$^+$ salts is advised. In general, total replacement needs 1 to 2 mmol/kg daily. In patients with nephrolithiasis, potassium citrate therapy reduces urine calcium excretion and stone formation rates (22).

Potassium must be given more rapidly to patients with severe or symptomatic hypokalemia. Hypokalemia should be corrected before alkali therapy because alkali therapy will aggravate hypokalemia by driving potassium into the cells and bicarbonaturia.

In conclusion, when the patients presented with hypokalemic paralysis, we should evaluate whether they were having renal or extra-renal K$^+$ wasting. Immunological investigations for SS should be provided in dRTA. Early recognition and prompt therapy for SS not only terminates potentially life-threatening hypokalemic paralysis but also prevents long-term complications related to SS.

References