Hypokalemic Paralysis as a Presenting Manifestation of Primary Sjögren’s Syndrome Accompanied by Vitamin D Deficiency

Chen-Yi Liao, Chih-Chiang Wang, I-Hung Chen, Jeng-Chuan Shiang, Mei-Yu Liu and Ming-Kai Tsai

Abstract

Primary Sjögren’s syndrome (pSS) is a chronic autoimmune disease characterized by progressive lymphocyte infiltration of the exocrine glands. Overt or latent renal tubular acidosis (RTA) is a common extraglandular manifestation of pSS. Vitamin D deficiency is associated with autoimmune disorders; however, the potential correlation between pSS and vitamin D deficiency is rarely discussed. The current patient presented with distal RTA, hypocalcemia, and hypophosphatemia that were found to be secondary to both vitamin D deficiency and pSS. In patients diagnosed with both distal RTA and vitamin D deficiency, clinicians should consider autoimmune diseases such as pSS, as a possible underlying etiology.

Key words: Sjögren’s syndrome, vitamin D deficiency, renal tubular acidosis, hypokalemic paralysis, autoimmune diseases

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Introduction

Primary Sjögren’s syndrome (pSS) is a disease of the exocrine glands that presents with dry eyes and mouth. Extraexocrine organ systems may also be involved, including the skin, lungs, gastrointestinal tract, nervous system, muscular skeletal apparatus, and kidneys (1). The reported rate of renal involvement in patients with pSS is variable, ranging from 2-67% (2). The spectrum of renal disease includes interstitial nephritis, renal tubular acidosis (RTA), tubular proteinuria, nephrogenic diabetes insipidus, glomerulonephritis, and renal failure (3). The most common manifestations are related to tubular dysfunction resulting from chronic interstitial nephritis with prominent CD+ T lymphocyte infiltration (4). RTA is the most common finding in Chinese pSS patients with renal involvement (5). Furthermore, hypokalemia is the most common electrolyte abnormality in RTA patients. The mechanism of underlying pSS-related RTA can be attributed to the complete absence of H-ATPase pumps in the intercalated cells (6) or autoantibodies directed against carbonic anhydrase II, which is associated with an impaired distal tubular transporter function (7). Abnormal vitamin D metabolism has been reported in pSS patients (8). However, the potential correlations between vitamin D deficiency and pSS have not been thoroughly investigated. We herein present a case of pSS with both RTA and vitamin D deficiency.

Case Report

A 49-year-old Chinese man presented to the emergency department with paralysis of all extremities upon awakening in the morning. His past medical records revealed intermittent, periodic, hypokalemic paralysis. Initially, no sicca symptoms were reported. Under the assumption of a diagnosis of RTA, additional drug and toxin surveys were performed at our nephrology outpatient department, resulting in negative findings. The patient had taken potassium citrate (10 gm QD) and spironolactone (25 mg bid) for hypokalemic paralysis. However, he did not attend follow-up visits for four months prior to admission, due to his busy schedule.
perphosphaturia (FEPO4, 9.7%) and hypocalcemia (7.9 mg/dL). The patient also had hypophosphatemia (1.6 mg/dL) with hy-
potension (urea nitrogen, 15 mg/dL; creatinine, 1.4 mg/dL),
which was the most prominent abnormality.

Profound hypokalemia (K⁺, 2.7 mmol/L) was the most
common finding. A urinalysis revealed a pH of 7.0 with protein (-). The total protein (6.4-8.3 mg/dL), albumin (3.4-4.8 mg/dL), and A/G ratio (1.2-2.4) were within the
normal range. A thorough investigation of the underlying
cause revealed xerostomia (the need for liquids to
swallow dry foods), xerophthalmia (a foreign body sensation
in the eyes), positive anti-Ro and anti-La antibodies, a high
antinuclear antibodies (ANA) titer (1:2,560, speckled), de-
layed saliva excretion on salivary scintigraphy, and a posi-
tive Schirmer’s test (<5 mm/5 min). Based on these results,
the patient met the diagnostic criteria for pSS and was
placed on potassium citrate (45 mEq/d) and active vitamin
D3 (0.25 μg/d) therapy to treat the hypokalemia and vitamin
D deficiency, respectively. The patient refused additional
steroids, chemotherapy, and renal biopsies. He experienced
no further sicca symptoms or paralysis during outpatient
department follow-up treatment with potassium citrate and
active vitamin D3.

Discussion

The present patient met the American-European classifica-
tion criteria for pSS. Ingested and cutaneously produced vi-
tamin D is rapidly converted to 25-hydroxyvitamin D [25
(OH)D or calcidiol]; however, only a fraction of 25(OH)D is
converted to its active metabolite, 1,25-dihydroxyvitamin D
[1,25(OH)2D; calcitriol]. Therefore, measuring the total 25
(OH)D level is the best test for assessing the amount of
stored vitamin D. Vitamin D deficiency is defined as a 25
(OH)D level of <20 ng/mL (9). In our case, the 25(OH)D
level was 16.9 ng/mL, confirming the diagnosis of vitamin
D deficiency.

The causes of vitamin D deficiency include reduced syn-
thesis of vitamin D in the skin (caused by sunscreen use,
skin pigmentation, aging, seasonal weather, latitude, time of
day, and skin grafts used to treat burns), decreased bioavail-
ability (malabsorption), increased catabolism (often caused
by medications, such as glucocorticoids or anticonvulsants),
breast feeding, decreased synthesis of 25(OH)D due to liver
failure, increased urinary excretion of 25(OH)D (caused by
nephrotic syndrome), and acquired disorders (such as tumor-
induced osteomalacia, primary hyperparathyroidism, granu-
Iomatous disorders, and hyperthyroidism). Some heritable
forms of rickets include: pseudo-vitamin D deficiency rick-
tets (vitamin D-dependent rickets type 1), autosomal domi-
nant hypophosphatemic rickets, and X-linked hypophos-
phatic rickets. All of these potential causes of vitamin D
deficiency were excluded in this case. Another mechanism,
in which 25(OH)D is metabolized by macrophages resulting
in a decreased 25(OH)D level, associated with autoimmune
disorders (8, 9). Like vitamin D deficiency, RTA has hun-
dreds of possible etiologies. It is possible for two unrelated,
distinct diseases to exist in a single patient. For concurrent
RTA and vitamin D deficiency, only a few potential causes,
including autoimmune disease and Fanconi’s syndrome,
have been described. Fanconi’s syndrome was excluded in
this case due to the lack of proteinuria, aminoaciduria, and
glycosuria and the normal uric acid level. A diagnosis of
pSS with RTA associated with vitamin D deficiency was
therefore highly probable in this case.

Abnormal vitamin D metabolism has rarely been reported

Table. Laboratory Parameters When at OPD and Admission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OPD</th>
<th>Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (7.35-7.45)</td>
<td>7.266</td>
<td>7.281</td>
</tr>
<tr>
<td>HCO₃⁻ (22-28 mmol/L)</td>
<td>18.8</td>
<td>21.0</td>
</tr>
<tr>
<td>Na⁺ (136-145 mmol/L)</td>
<td>144.2</td>
<td>141.5</td>
</tr>
<tr>
<td>K⁺ (3.5-5.1 mmol/L)</td>
<td>2.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Ca²⁺ (8.4-10.2 mmol/dL)</td>
<td>7.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Phosphate (2.4-4.5 mg/dL)</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Uric acid (3.4-7 mg/dL)</td>
<td>3.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Glucose (70-105 mg/dL)</td>
<td>111</td>
<td>94</td>
</tr>
<tr>
<td>BUN (7-20 mg/dL)</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Creatinine (0.7-1.2 mg/dL)</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Total protein (6.4-8.3 mg/dL)</td>
<td>6.5</td>
<td>6.9</td>
</tr>
<tr>
<td>Albumin (3.4-4.8 mg/dL)</td>
<td>3.3</td>
<td>3.9</td>
</tr>
<tr>
<td>A/G ratio (1.2-2.4)</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>ANA (0-1:1000000)</td>
<td>None</td>
<td>&gt;240</td>
</tr>
<tr>
<td>Rheumatoid factor (0-15 IU/mL)</td>
<td>23.4</td>
<td>16.8</td>
</tr>
</tbody>
</table>
| AntiRo/La (<7 U/mL; nega-
 tive: >10 U/mL; positive) | None      | 92        |
| C3 (86-160 mg/dL)          | None      | 92        |
| C4 (17-45 mg/dL)           | None      | 23        |
| IgG (750-1560 mg/dL)       | None      | None      |
| Urinalysis                 | None      | None      |
| Glucose (mmol/L)           | (-)       | (-)       |
| Protein (g/L)              | (-)       | (-)       |
| Urine NAG                  | None      | None      |

as a marble stone worker. The patient reported normal die-
tary habits with three meals per day consisting predomin-
antly of rice. He claimed no history of vomiting, diarrhea,
use of Chinese herbs, chemotherapy agents, or steroids. He
also did not have hyperthyroidism.

On admission, the blood cell count was within the normal
range. A urinalysis revealed a pH of 7.0 with protein (-). Profound hypokalemia (K⁺, 1.9 mmol/L) with renal K⁺ wast-
ing (urine K⁺: Cr ratio, 4.44 mmol: mmol; transtubular po-
tassium concentration gradient, TTKG 8.2) was the most
prominent abnormality.

Hyperchloremic metabolic acidosis associated with a pos-
tive urinary anion gap (low ammonium excretion), alkaline
urinary pH (>5.5), and renal stones strongly suggested the
presence of distal RTA. In addition to an abnormal renal
function (urea nitrogen, 15 mg/dL; creatinine, 1.4 mg/dL),
the patient also had hypophosphatemia (1.6 mg/dL) with hy-
perphosphaturia (FEPO4, 9.7%) and hypocalcemia (7.9 mg/dL).
The laboratory findings are shown in Table. An electro-
cardiogram disclosed no obvious abnormalities. Abdominal
sonography revealed multiple bilateral renal stones. The pa-
tient’s muscle strength recovered following aggressive KCl
supplementation (a rate of 10 mEq/h for 24 hours), after
which he received oral potassium citrate (45 mEq/d).

Due to hypophosphatemia (1.6 mg/dL) accompanied by
hypocalcemia (7.9 mg/dL) and mildly elevated iPTH (92.2
pg/mL), a vitamin D test was performed, which showed a
25-hydroxyvitamin D [25(OH)D] level of 16.9 ng/mL (nor-
mal range, >30 ng/mL), thereby confirming the diagnosis of
vitamin D deficiency. A thorough investigation of the under-
lying cause revealed xerostomia (the need for liquids to

a
in pSS patients (8). Vitamin D may play a role in the pathogenic process and disease expression of pSS and is generally an important environmental factor that can increase the prevalence of certain autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus, and inflammatory bowel disease (9, 10). Zold et al. reported that, in their study, individuals with undifferentiated connective tissue disorders who progressed to rheumatoid arthritis (34.2%), lupus (17.1%), Sjögren’s syndrome (17.1%), or mixed connective tissue disease (17.1%) had lower vitamin D levels than individuals who did not progress beyond the undifferentiated connective tissue disease stage (11). In recent years, the discovery of the nuclear vitamin D receptor (VDR) expression in immune cells and the finding that some immune cells can produce the vitamin D hormone have suggested that vitamin D possesses immunoregulatory properties (9, 12). Alternatively, pSS, which results from polyclonal B cell activation, may itself have contributed to the low concentration of 25(OH)D observed in this case because 25(OH)D is metabolized in activated monocytes and consumed by activated lymphocytes by binding to vitamin D receptors (8). The relationship between vitamin D deficiency and autoimmune disease brings to mind the “chicken and egg” scenario: which comes first, vitamin D deficiency or autoimmunity? Currently, the evidence remains inconclusive.

Patients with concurrent RTA, hypocalcemia, and hypophosphatemia should undergo vitamin D testing. If vitamin D deficiency is confirmed in patients with RTA, further autoimmune testing should be performed due to the close correlation between vitamin D deficiency and autoimmunity. Vitamin D deficiency is linked to the disease activity in new cases of systemic lupus erythematosus and warrants prompt vitamin D supplementation (13). Vitamin D treatment has been shown to improve in autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, and psoriasis (12, 14). Concurrent pSS and vitamin D deficiency increases the risk for peripheral neuropathy, lymphoma, osteomalacia, and even multiple bone fractures (15, 16). The mainstay of treatment for pSS with vitamin D deficiency is the maintenance of the acid-base and electrolyte balance, with further treatment aimed at ameliorating the underlying disease. Potassium citrate and active vitamin D can be administered to correct metabolic acidosis, hypokalemia, and hypophosphatemia and prevent further nephrocalcinosis.

Based on our case, we conclude that patients diagnosed with both RTA and vitamin D deficiency should be considered highly likely to have some type of autoimmune disease, such as pSS. Early diagnosis lead to the more rapid initiation of the correct course of treatment, including vitamin D supplementation, and improve patient outcomes.

The authors state that they have no Conflict of Interest (COI).

References