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

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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 CD⁴⁺ 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

Table. Laboratory Parameters When at OPD and Admission

	OPD	Admission
pH (7.35-7.45)	7.266	7.281
HCO ₃ ⁻ (22-28mmol/L)	18.8	21.0
Na ⁺ (136-145mmol/L)	144.2	141.5
K ⁺ (3.5-5.1mmol/L)	2.7	1.9
Cl ⁻ (98-107mmol/L)	114.4	110.7
Ca ²⁺ (8.4-10.2mg/dL)	7.8	7.9
Phosphate(2.4-4.5mg/dL)	2.1	1.6
Uric acid(3.4-7mg/dL)	3.3	5.2
Glucose(70-105mg/dL)	111	94
BUN (7-20mg/dL)	14	15
Creatinine (0.7-1.2mg/dL)	1.1	1.4
Total protein (6.4-8.3mg/dL)	6.5	6.9
Albumin (3.4-4.8mg/dL)	3.3	3.9
A/G ratio (1.2-2.4)	1.0	1.3
ANA	1:320	1:2,560
Rheumatoid factor (0-15 IU/mL)	23.4	16.8
AntiRo/La(<7U/mL; negative;>10U/mL;positive)	None	>240/>320
C3(86-160 mg/dL)	None	92
C4(17-45 mg/dL)	None	23
IgG (750-1,560mg/dL)	None	None
Urinalysis		
Glucose(-)	(-)	(-)
Protein(-)	(-)	(-)
Urine NAG	None	None

as a marble stone worker. The patient reported normal dietary habits with three meals per day consisting predominantly 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⁺ wasting (urine K⁺: Cr ratio, 4.44 mmol: mmol; transtubular potassium concentration gradient, TTKG 8.2) was the most prominent abnormality.

Hyperchloremic metabolic acidosis associated with a positive 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 hyperphosphaturia (FE_{PO4}, 9.7%) and hypocalcemia (7.9 mg/dL). The laboratory findings are shown in Table. An electrocardiogram disclosed no obvious abnormalities. Abdominal sonography revealed multiple bilateral renal stones. The patient'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 (normal range, >30 ng/mL), thereby confirming the diagnosis of vitamin D deficiency. 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), delayed saliva excretion on salivary scintigraphy, and a positive 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 classification criteria for pSS. Ingested and cutaneously produced vitamin 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 synthesis 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 bioavailability (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, granulomatous disorders, and hyperthyroidism). Some heritable forms of rickets include: pseudo-vitamin D deficiency rickets (vitamin D-dependent rickets type 1), autosomal dominant hypophosphatemic rickets, and X-linked hypophosphatemic 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 hundreds 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

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 D₃ 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).

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