Case Report

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Recurrent Severe Hyponatremia in a Patient with Sjögren's Syndrome

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Sjögren's syndrome (SS) is an autoimmune disease that presents with exocrine gland dysfunction. Renal involvement is common in SS and often results in tubulointerstitial nephritis, renal tubular acidosis, and Fanconi's syndrome. Electrolyte imbalances are commonly the first symptom of renal involvement of SS. The most common feature of dysnatremia in SS is hypernatremia with diabetes insipidus. However, cases of hyponatremia with syndrome of inappropriate antidiuretic hormone secretion (SIADH) are rarely reported in patients with SS. Herein, we report a case of recurrent severe SIADH in a patient with SS.

Key Words: Duloxetine hydrochloride, Hyponatremia, Inappropriate ADH syndrome, Sjögren's syndrome

Introduction

Sjögren's syndrome (SS) is an autoimmune disease that presents with symptoms and signs of exocrine gland dysfunction[1]. Targets are mostly salivary and lacrimal glands. As a result of the local inflammation of these glands, patients typically have ocular and oral dryness and salivary gland swelling[1]. Systemic involvements occur in approximately one-third of patients with SS. Lymphocytic infiltration and inflammation can cause various complications including synovitis, cutaneous lupus, cerebral vasculitis, autoimmune primary biliary cholangitis, and obstructive bronchiolitis[1-4].

Renal involvement of SS is common and often results in tubulointerstitial nephritis (TIN), renal tubular acidosis (RTA), and Fanconi's syndrome. Glomerulonephritis rarely occurs and is associated with cryoglobulinemia[1,2,4]. Electrolyte imbalances are commonly the first symptom of renal involvement of SS and mostly are associated with tubulointerstitial dysfunction[4]. Central nervous system (CNS) involvement of SS can alter the hypothalamic-pituitary-adrenal (HPA) axis[5]. These alterations result in diabetes insipidus (DI) with hypernatremia[4]. However the development of syndrome of inappropriate antidiuretic hormone secretion (SIADH) in patients with SS is rare. Herein, we report a case of recurrent severe SIADH in a patient with SS.

Case Report

A 56-year-old woman with a background of SS was admitted to the hospital with complaints of nausea, dizziness, and anxiety.

When she was first diagnosed with SS 8 months before, she complained of dry mouth, fever, and salivary gland swelling. Laboratory test results were strongly positive for anti-SS-A antibody. Her serum sodium concentration of 124 mEq/L indicated hyponatremia. Treatment with systemic steroid and methotrexate did not improve her symptoms and hyponatremia. Three months later, treatment with an IL-6 receptor inhibitor, tocilizumab, was initiated. Consequently, her symptoms improved drama-

tically. Her hyponatremia was also corrected along with the tocilizumab treatment to recover the serum sodium concentration to 136 mEq/L.

She was taking 200-mg hydroxychloroquine, 12.5-mg methotrexate, and 1-mg folic acid, and was received tocilizumab every month. The administration of methylprednisolone 2 mg was discontinued 10 weeks before. Three days prior to her visit, she was given some medications, including clonazepam and duloxetine for palpitation and anxiety. She did not take any kind of diuretic.

At the initial presentation, her blood pressure was 133/72 mmHg, pulse rate was 70 times/minute, and body temperature was 36.1℃. On physical examination, her tongue was not dehydrated and skin turgor was normal. No hepatomegaly, splenomegaly, other palpable abdominal masses, and ascites were found. There were no abnormal findings suggesting cardiac failure. Jugular vein expansion and peripheral edema were not observed. Brain computed tomography (CT) revealed no abnormalities (Fig. 1). Her blood chemistry revealed the following values: sodium concentration, 112 mEq/L; chloride concentration, 76 mEq/L; osmolality, 231 mOsm/kg H_2O; plasma uric acid, 1.9 mg/dL; blood urea nitrogen, 8.8 mg/dL; and creatinine, 0.70 mg/dL. Brain natriuretic peptide concentration was 196.2 pg/mL, which suggested normal or reduced extracellular fluid volume. Urine biochemistry results showed a urine sodium concentration of 62 mEq/L and an osmolality of 298 mOsm/kg H_2O (Table 1). Her thyroid function was normal and serum ACTH and cortisol levels were within the normal limits. Inspite of the severe hypo-osmolar hyponatremia, her serum antidiuretic hormone (ADH) level was 4.39 pg/mL (Table 2).

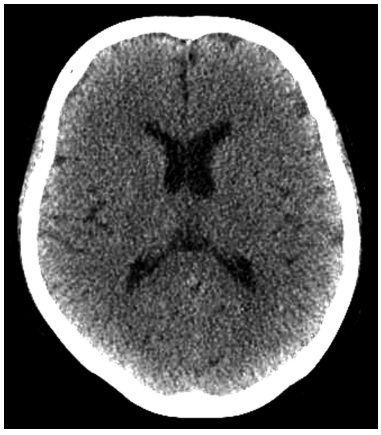

Fig. 1. Brain computed tomography.

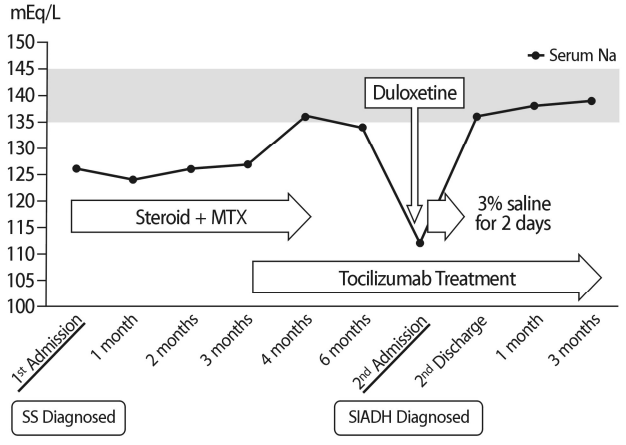

Fig. 2. Sodium concentration over time.

Table 1. Laboratory values on initial presentation

Laboratory Test	Values
Blood tests	
Glucose (mg/dL)	124
Urea Nitrogen (mg/dL)	8.8
Creatinine (mg/dL)	0.70
Sodium (mEq/L)	112
Potassium (mEq/L)	3.5
Chloride (mEq/L)	76
Uric acid (mg/dL)	1.9
Osmolality (mOsm/kg H_2O)	231
Urine tests	
Sodium (mEq/L)	62
Potassium (mEq/L)	33.4
Chloride (mEq/L)	59
Osmolality (mOsm/kg H_2O)	298
Total protein (mg/dL)	5.7
Creatinine (mg/dL)	31.8
Uric acid (mg/dL)	20.5

Table 2. Endocrinologic studies

Laboratory Test	Values	Reference range
TSH (uIU/mL)	2.749	0.55-4.78
Free T4 (ng/dL)	1.73	0.82-1.76
ACTH (pg/mL)	20.52	10.0-80.0
Cortisol (ug/dL)	12.16	9.52-26.2
ADH (pg/mL)	4.39	0.0-6.7

TSH, thyroid stimulating hormone; Free T4, free thyroxine; ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone.

She started receiving 3% saline, which improved her sodium concentration to 128 mEq/L over the next 2 days, and the clonazepam and duloxetine were discontinued. After correction of the symptomatic hyponatremia, intravenous (IV) fluid administration was stopped, dietary intake of salt was encouraged, and water intake was restricted to ≤1,000 mL/day. After that, the normal serum sodium concentration was maintained well without IV fluid administration, and the patient was discharged (Fig. 2).

Discussion

Renal involvement of SS has been reported to range from 5% to 14% in several European studies[6,7] and to >30% in a Chinese cohort study[8]. Its frequent presentation is tubular involvement with electrolyte disturbances[2,4]. Approximately two-thirds of patients with SS and renal dysfunction show TIN[4]. Advanced chronic kidney disease can result from TIN. Therefore, appropriate screening is required in these patients. TIN is also responsible for the occurrence of RTA and renal concentrating defect[4].

Approximately 2.5-60% of patients with SS have CNS manifestations[3]. The most common feature was headache followed by cognitive dysfunction and mood disorders[3,9]. Cerebral vasculitis and demyelinating lesions are relatively frequent[1,3]. Though rarely, lymphocytic infiltration of the hypothalamus or pituitary gland leads to impairment of the HPA axis[3,5,9]. The condition in which lymphocytic infiltration affects the infundibulum, is termed infundibuloneurohypophysitis and might cause central DI[9]. In our case, the patient's brain CT image showed normal hypophysis and no signs or symptoms of DI.

All of our patient's symptoms associated with severe hypo-osmolar hyponatremia with elevated serum ADH concentration were ameliorated by administration of hyperosmotic fluid with water restriction, which demonstrated that SIADH was the cause of her recurrent and severe hyponatremia. However, in patients with SS, only few reports have described cases of SIADH[10,11]. Recently, several research studies reported that inflammatory cytokines such as interleukin (IL)-1β or IL-6 are responsible for the development of SIADH[12]. Palin et al.[13] revealed that IL-6 brain injection increased the ADH neuron activity and anti-IL-6 antibody injection ameliorated the activation of ADH neurons in Wistar rats. Similar results were obtained by Mastorakos et al.[14] in humans. Six patients who received recombinant IL-6 therapy showed significantly increased serum ADH concentrations, which suggested that IL-6 activated ADH-secreting neurons. Inflammatory cytokines also contribute to the pathogenesis of SS[15]. The major inflammatory cytokines in SS are IL-1β, IL-6, IL-12, tumor necrosis factor-α, and interferons[4,12].

The cause of the first hyponatremia in the patient has not been sufficiently evaluated, but the clinical and laboratory features of the patient were fit for diagnosis of SIADH. In our patient, hyponatremia was not improved by steroid therapy, whereas tocilizumab made a complete recovery from hyponatremia. Juanita et al.[16] reported a case of SIADH in a patient with systemic juvenile idiopathic arthritis (SJIA) successfully treated with an IL-6 inhibitor, tocilizumab. They showed that the positive response to treatment with tocilizumab supports the role of IL-6 in the pathogenesis of both SJIA and SIADH[16]. The fact that steroid treatment was not responding and there was a positive response to tocilizumab treatment in hyponatremia in our patient suggest that tocilizumab has a main role on hyponatremia in the patient.

The second hyponatremia was fully evaluated and was caused by SIADH. At that point, the disease was well controlled with tocilizumab therapy, without other aggravated symptoms of SS. Moreover, the patient had a history of taking duloxetine for 3 days, and after discontinuation of duloxetine, the hyponatremia was improved. Many drugs are known to cause SIADH, such as antidepressants, anticonvulsants, antipsychotics, and pain killers[17,18]. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is widely used to treat major depressive disorders, fibromyalgia, and diabetic neuropathy[18,19] and causes SIADH[18,19]. Older age, female sex, a history of hyponatremia, diuretic use, and low body weight are high-risk factors of duloxetine-induced hyponatremia[19]. In the present case, the patient was female and had a history of hyponatremia.

These findings indicate that SS could be a cause of

SIADH. Therefore, awareness of the possibility of SIADH in patients with SS is important for accurate treatment.

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