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【 CASE REPORT 】

Early Relowering of Serum Sodium Concentration Overcomes Disturbances in Consciousness during Hyponatremia Overcorrection and Prevents Osmotic Demyelination Syndrome

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Abstract:
A 79-year-old woman without any cerebral hernia symptoms was hospitalized with hyponatremia. After syndrome of inappropriate antidiuretic hormone induced by drugs was diagnosed and water restriction implemented, the patient became comatose during overcorrection caused by the generation of a large volume of electrolyte-free urine. Once the serum sodium concentration was immediately relowered by the administration of desmopressin and 5% glucose solution, the patient's level of consciousness improved dramatically without osmotic demyelination syndrome (ODS) developing. This outcome suggests that, similar to the findings in rat models, relowering the serum sodium concentration as early as possible to counter a disturbance of consciousness during the overcorrection of hyponatremia prevents ODS.

Key words: osmotic demyelination syndrome, relowering of serum sodium concentration, syndrome of inappropriate ADH, hyponatremia, rat model

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Introduction

Hyponatremia occurs in up to 30% of hospitalized patients (1, 2). In contrast, overly rapid increases in the serum sodium concentration leads to osmotic demyelination syndrome (ODS) of unknown incidence (3) with a potentially serious outcome. For example, in a recent ODS study, a third of patients recovered, a third were debilitated but still independent, and a third were dependent (4). It is suggested that an overly rapid correction occurs more readily when treatment of the underlying cause restores the kidney's capacity to excrete electrolyte-free water. Examples of such situations include withholding drugs known to cause the syndrome of inappropriate antidiuretic hormone (SIADH) (5-7), withholding thiazides (8), the treatment of a glucocorticoid deficiency (9), and volume repletion in hypovolemia (10). A previous study reported that ODS developed two to six days after the excessive correction of hyponatremia (11, 12). In the present case, a patient diagnosed with SIADH became comatose during a rapid correction, and her impaired consciousness was improved by the prompt relowering of the serum sodium concentration.

Case Report

A 79-year-old woman had a 20-day history of anorexia and malaise. Hyponatremia of 130 mEq/L was observed by her family doctor. The hyponatremia worsened to 126 and 120 mEq/L after 7 and 15 days, respectively. When the patient visited our hospital, her serum sodium concentration was determined to be 112 mEq/L, and she was subsequently admitted. Parkinson's disease and paroxysmal atrial fibrillation, hypertension, and anxiety neurosis were recognized in her medical history. The following medicines were administered orally: pramipexole 0.375 mg, levodopa 300 mg, benserazide 75 mg, eszopiclon 2 mg, xarelto 15 mg, bisoprolol 2.5 mg, benidipine 2 mg, mirtazapine 15 mg, and clotiazepam 5 mg. On a physical examination, her consciousness on the Glasgow Coma Scale (GCS) was E3-V4-M6, body tem-

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Table. Laboratory Findings. Findings for Blood Biochemistry, a Complete Blood Count, and a Urinalysis Performed at Admission. The Endocrinological Data are from the Fourth Day of Hospitalization.

Blood biochemistry		(reference range)	*Complete blood count*		(reference range)
Total protein	7.0 g/dL	(6.7-8.3)	WBC	10,900 /μL	(3,500-9,000)
Albumin	4.1 g/dL	(4.0-5.0)	Hemoglobin	13.6 g/dL	(12.0-16.0)
AST	20 IU/L	(13-33)	Platelets	387,000 /μL	(14-35×10^4)
ALT	12 IU/L	(6.0-30)			
Total bilirubin	1.6 mg/dL	(0.3-1.2)	*Urinalysis*		
ALP	150 IU/L	(115-359)	Gravity	1.015	(1.01-1.025)
			Osmolality	458 mOsm/kg	
UA	1.1 mg/dL	(2.5-7.0)	Na	124 mEq/L	
BUN	9.0 mg/dL	(8-22)	K	38 mEq/L	
Cr	0.38 mg/dL	(0.47-0.79)	Cr	49 mg/dL	
Na	112 mEq/L	(138-146)			
K	2.2 mEq/L	(3.6-4.9)	*Endocrinological data (day 4, Na 120 mEq/L)*		
Cl	78 mEq/L	(99-109)	ADH	1.8 pg/mL	(0.0-0.0)
Ca	8.5 mg/dL	(8.7-10.3)	ACTH	31 pg/mL	(7.2-63.3)
P	2.5 mg/dL	(2.5-4.7)	Cortisol	22 μg/dL	(6.2-18.0)
Mg	2.4 mg/dL	(1.6-2.6)	TSH	1.5 μIU/mL	(0.35-4.94)
			Free T3	2.6 pg/mL	(1.71-3.71)
Plasma glucose	160 mg/dL	(70-109)	Free T4	1.3 ng/dL	(0.7-1.48)
Tryglyceride	104 mg/dL	(30-149)	Renin	0.2 ng/mL/h	(0.3-5.4)
CRP	0.02 mg/dL	(0.0-0.30)	Aldosterone	55 pg/mL	(35.7-240)
Calculated osmolality	236 mOsm/kg				

AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, UA: uric acid, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, WBC: white blood cell, ADH: antidiuretic hormone, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, T3: triiodothyronine, T4: thyroxine

perature was 36.6℃, blood pressure was 111/67 mmHg, pulse was 85 beats/minute, and peripheral oxygen saturation (SpO_2) was 96%. The patient's skin was well-hydrated, and the oral cavity was wet. Regarding the chest findings, the lung sounds were clear, and no murmur was heard. The lower extremities did not show edema. Manual muscle testing of the limbs showed results of 4/5. The laboratory findings are shown in Table. Pulmonary congestion was not obvious on chest X-ray, and electrocardiogram showed a normal sinus rhythm. Computed tomography findings of the head and chest were normal.

At hospital admission, hyponatremia (112 mEq/L) with a calculated plasma osmotic pressure of 236 mOsm/kg without symptoms of cerebral hernia was observed. With regard to the hyponatremia, the patient's circulating plasma volume and renal function were normal, and a diuretic was not used. Her urinary osmotic pressure (458 mOsm/kg) and sodium concentration (124 mEq/L) were high, suggesting drug-induced SIADH by pramipexole and mirtazapine, adrenal cortical dysfunction, or hypothyroidism as possible causes. Her adrenal cortical and thyroid functions were later found to be normal, so the patient was diagnosed with SIADH.

The course after admission is shown in Fig. 1. The patient visited the hospital at 12:00 and entered the intensive-care unit. During treatment, pramipexole and mirtazapine were discontinued, and water restrictions (0.9% NaCl 20 mL/h) was initiated. Her consciousness was GCS:E3-V4-M6 until 16:30, subsequently deteriorating to GCS:E1-V3-M5 at 17:00 and to GCS: E1-V1-M4 at 18:00. The overcorrection of the serum sodium concentration (from 112 to 126 mEq/L; Δ sodium=14 mEq/5 hours) was measured. Urination at 1,500 mL/5 hours was observed, and the urine was found to be electrolyte-free (osmotic pressure: 83 mOsm/kg, sodium concentration: 6.7 mEq/L). To promptly relower the serum sodium concentration, a 5% glucose solution at 500 mL/h was started, and a 60 μg desmopressin acetate hydrate tablet was administered. At 19:00, because the tablet remained undissolved, a 5 μg desmopressin acetate hydrate spray was administered. The urine volume decreased at 20:00, the serum sodium concentration declined from 126 to 120 mEq/L, and her consciousness improved to GCS: E3-V4-M6. The correction rate of the serum sodium concentration was subsequently kept below 8 mEq/24 hours using a 60 μg desmopressin acetate hydrate tablet at a urine volume of ≥150 mL/h with adjustment of the replacement fluid. On day 6 of hospitalization, the serum sodium concentration improved to 133 mEq/L, and the patient started eating; replacement fluid and the administration of desmopressin acetate hydrate tablets was stopped. The serum sodium concentration stabilized with water restriction of 500 mL/h. Head magnetic resonance imaging performed on days 1 (at 19:00), 7, and 15 of hospitalization for the evaluation of the ODS were normal (Fig. 2). The patient was discharged on day 22 of hospitalization without sequelae.

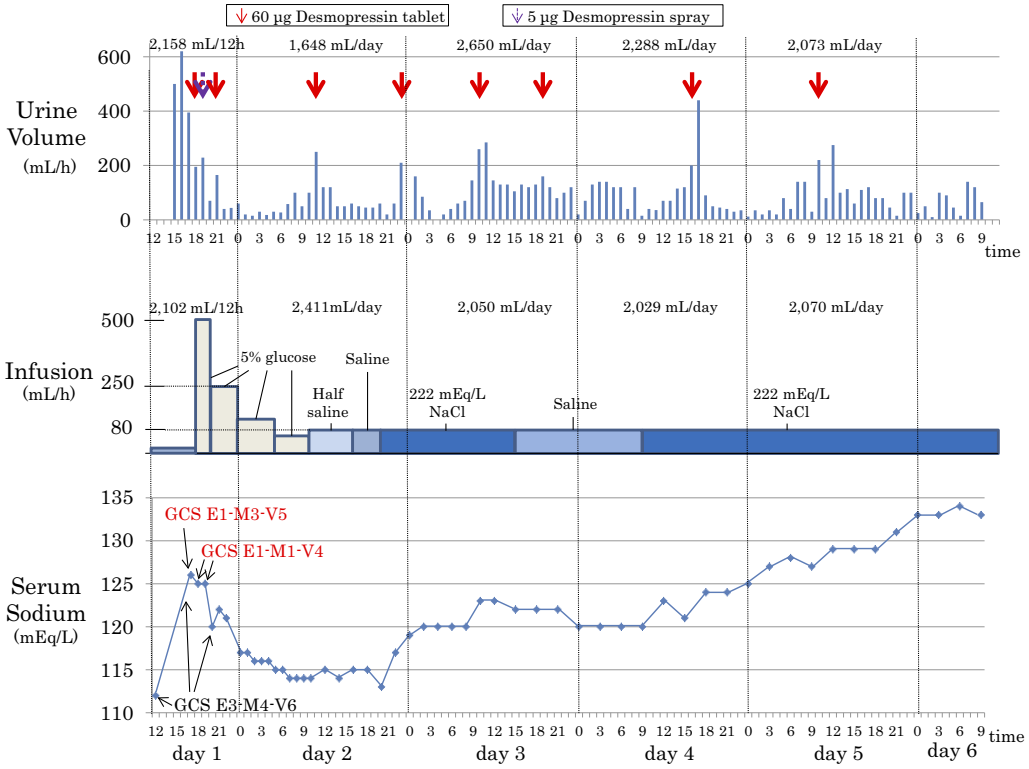

Figure 1. **The change in the urine volume, replacement fluid content, and serum sodium concentration from the 1st to the 5th day of hospitalization. The patient's state of consciousness is reflected by the graph of the serum sodium concentration. The solid arrow indicates the administration of a 60 μg desmopressin tablet. The dotted arrow indicates the administration of a 5 μg desmopressin spray. GCS: Glasgow Coma Scale**

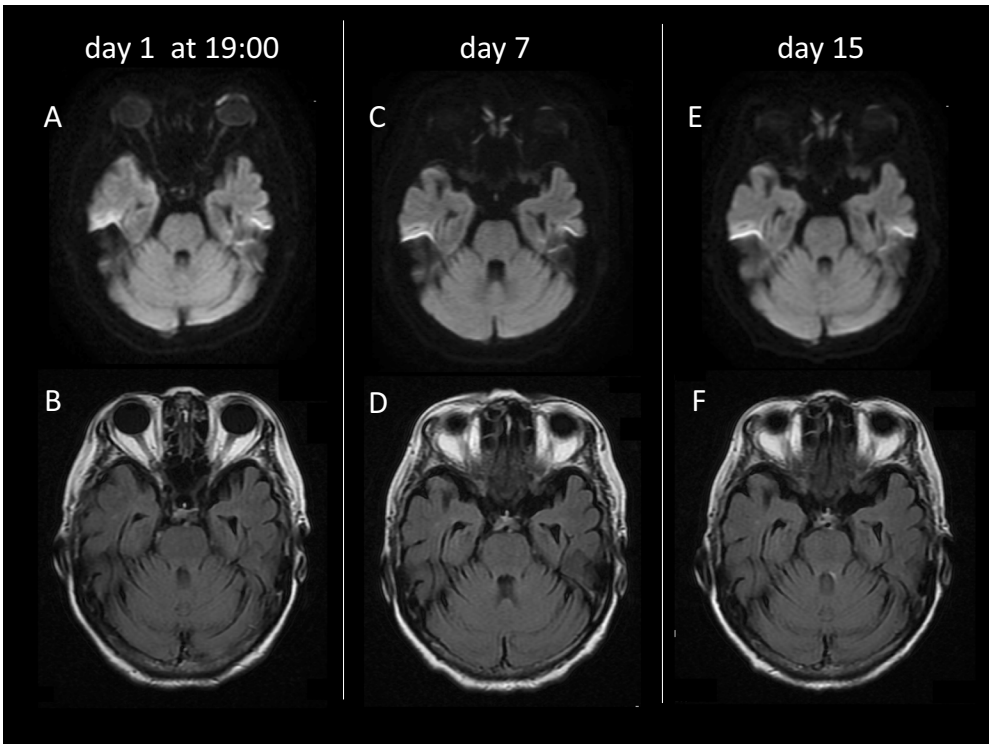

Figure 2. **Head magnetic resonance imaging findings. The findings from imaging performed on days 1 (at 19: 00), 7, and 15 of hospitalization for the evaluation of the ODS were normal. A, C, and E are diffusion-weighted imaging (DWI). B, D, and F are fluid-attenuated inversion recovery (FLAIR).**

Discussion

For the treatment of this case, we followed the clinical practice guidelines for the diagnosis and treatment of hyponatremia recommended by the European Society of Endocrinology, European Society of Intensive Care Medicine, European Renal Association European Dialysis and Transplant Association (3). Our patient was diagnosed with SIADH, and water restriction was consequently started. The overcorrection of the serum sodium concentration was confirmed after 5 hours based on the large volume of electrolyte-free urine. Regarding the management of overcorrection, prompt intervention to relower the serum sodium concentration if it increases >10 mEq/L during the first 24 hours is recommended (3). To this end, the infusion of 10 mL/kg body weight of electrolyte-free water (e.g. glucose solution) over 1 hour with strict monitoring of the urine output and fluid balance is recommended, along with the administration of desmopressin (3). We reduced the serum sodium concentration using glucose solution and a desmopressin tablet, and subsequent correction was also performed using a desmopressin tablet.

In the present case, although the patient fell into a coma due to the overcorrection of hyponatremia, her disturbance of consciousness was improved following the prompt relowering of the serum sodium concentration. In addition, ODS did not subsequently develop. Although there are limited reports in humans in such case, many reports are available in animal models. It has been suggested that the relowering of sodium at an early stage may help prevent ODS when a disturbance of consciousness is observed immediately after the overcorrection of hyponatremia. When rats are subjected to a large and rapid correction (Δ serum sodium concentration = approximately 30 mEq/L/12 hours), the incidence of death within 12 hours is 20% (13). In the present patient, we observed a large and rapid overcorrection (Δ serum sodium concentration=14 mEq/L/5 hours), suggesting that the neurological abnormality may have occurred early. In the rat model, the survival rate of the group in which neurological symptoms appeared within 24 hours of an overcorrection of the serum sodium concentration was remarkably low at 7.6% (14). However, reducing the serum sodium concentration within 8 hours after symptoms appeared significantly increased the survival rate to 47%. Furthermore, it was suggested that the faster the timing of the relowering (2-4 hours vs. 4-8 hours), the higher the survival rate (2-4 hours group: 55% vs. 4-8 hours group: 33%). A pathological analysis in the surviving rats revealed that ODS was observed in the non-relowered group, but only 2/7 cases had ODS in the relowered group. Early neurological manifestations, which were ruled out as being due to demyelination (myelin degeneration is a more progressive process), were the first clinical manifestations of brain lesions that ultimately led to myelinolysis. Consequently, this also suggested that the process might be reversible (14).

In six clinically reported cases of the overcorrection of hyponatremia without neurological abnormalities, preventive relowering of sodium did not result in ODS (15). In addition, although ODS occurred when correcting hyponatremia (5 mEq/L/day for 3 days), the neurological abnormalities were completely improved with the subsequent reduction of the sodium level (16). The benefits and harms of active treatments to relower the serum sodium concentration in cases of overly rapid correction have not been well studied (3). Nevertheless, the guideline development group feels that the dramatic consequences of ODS warrant active intervention to re-lower the serum sodium concentration in cases of overly rapid correction (3).

In summary, although this patient became comatose during the overcorrection of her hyponatremia, her consciousness disorder improved by the prompt relowering of the serum sodium concentration, and ODS did not develop. In a rat model, a disturbance of consciousness that is recognized immediately after an overcorrection is accompanied by a poor prognosis. However, this neurological abnormality is reversible with the early reduction of the serum sodium concentration. These facts suggest that relowering the serum sodium concentration as soon as possible should be considered in cases where a disturbance of consciousness is observed during the overcorrection of hyponatremia.

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

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