

## The Improvement of the Outcome of Osmotic Demyelination Syndrome by Plasma Exchange

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### Abstract

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A 71-year-old Japanese woman presented with progressive fatigue, lethargy, dysarthria and a gait disorder. Her laboratory data revealed hyponatremia (Na 101 mEq/L), and we started correcting her serum sodium level. Within a few days, she became comatose, bedridden, and was intubated. We diagnosed osmotic demyelination syndrome (ODS) and started performing plasma exchange (PE) on the 39th day of hospitalization. She fully recovered after starting PE, and was discharged on foot unassisted. PE can be a beneficial treatment in patients with chronic ODS.

**Key words:** osmotic demyelination syndrome, hyponatremia, plasma exchange

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### Introduction

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Osmotic demyelination syndrome (ODS), which is also known as central pontine myelinolysis (CPM), has been found to occur after the rapid correction of severe hyponatremia (1). The clinical manifestations of ODS are known to develop for 2-6 days after a rapid elevation of the serum sodium level. The symptoms are often irreversible or only partially reversible, and they include dysarthria, dysphagia, tetraparesis, behavioral disturbances, lethargy, confusion, disorientation, and coma (2).

When CPM develops after the rapid correction of hyponatremia, plasma exchange (PE) may be a beneficial therapy. Bibl et al. successfully treated three young female patients by intensive plasmapheresis soon after confirming a diagnosis of CPM (3). All three patients had undergone the correction of severe hyponatremia at 3-5 days before the onset of the neurological symptoms. Significant clinical improvement was obtained at one month after the start of plasmapheresis. We herein report a case of chronic ODS that was successfully treated by PE.

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### Case Report

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A 71-year-old Japanese woman with hypertension and dyslipidemia was admitted for progressive dysarthria and gait disorder. She had experienced progressive fatigue and lethargy for a few weeks. She had been taking nifedipine CR (40 mg/day), imidapril (10 mg/day), valsartan (80 mg/day), rosuvastatin (2.5 mg/day), trichlormethiazide (4 mg/day), zolpidem (10 mg/day), teprenone (1.5 g/day), magnesium oxide (990 mg/day), torimebuciren (300 mg/day), for a few years. She looked confused but was aware of her name, and the place and time. She denied any recent episodes of a cold or weight loss. She was 154 cm in height, and weighed 57 kg. Her vital signs were within the normal limits. She was slightly edematous in the lower extremities. There were numerous bruises all over her body as a result of repeated falls. A neurological examination revealed dysarthria, drooling and unsteadiness in balance and gait. The laboratory data on admission is shown in the Table; briefly, hyponatremia (Na 101 mEq/L), hypochloremia (Cl 68 mEq/L), and slight hypokalemia (K 3.5 mEq/L). Head computed tomography (CT) and brain magnetic resonance imaging (MRI) revealed no abnormalities, and electrocardiography

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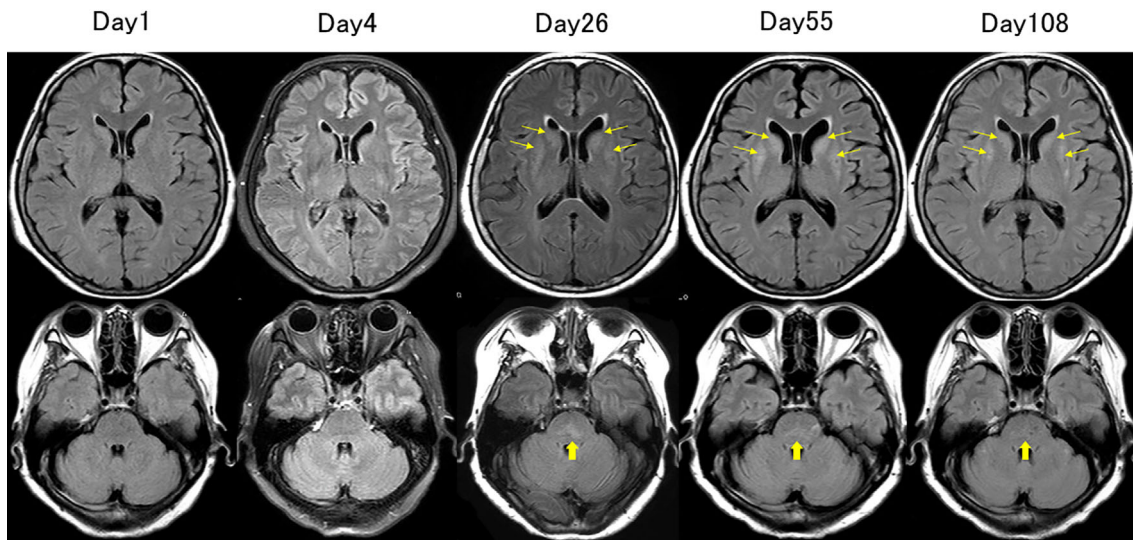
**Table. The Laboratory Findings.**

Urinalysis		Blood chemistry		Immunology	
specific gravity	1.010	HbA1c	5.9 %	IgG	937 mg/dL
pH	6.0	TP	7.1 g/dL	IgA	117 mg/dL
protein	±	AST	90 IU/L	IgM	72 mg/dL
occult blood	2+	ALT	64 IU/L	CH50	35 IU/mL
Sediments		LDH	574 IU/L	C3	68 mg/dL
RBC	5-9 /HPF	CK	2023 IU/L	C4	28 mg/dL
		BUN	9.5 mg/dL	ANA	× 80
uOSM	202 mOSM/kg	Cr	0.41 mg/dL	<b>Others</b>	
uUN	229 mg/dL	Na	101 mEq/L	TSH	1.63 μIU/mL
uNa	14 mEq/L	K	3.5 mEq/L	free T3	1.91 pg/dL
uK	10.6 mEq/L	Cl	68 mEq/L	free T4	1.75 ng/dL
uCl	21 mEq/L	Ca	8.5 mg/dL	hANP	32.7 pg/mL
uCr	37.4 mg/dL	TG	41 mg/dL	PRA	6.5 ng/mL/hr
		HDL	102 mg/dL	aldosterone	117 pg/mL
		LDL	35 mg/dL	ACTH	28.9 pg/mL
<b>Complete blood count</b>		CRP	0.74 mg/dL	cortisol	20.3 μg/dL
WBC	11650 /μL	eGFR	111.9 mL/min/1.73m <sup>2</sup>	AVP	2.6 pg/mL
Neutrophils	80.4 %	pOsm	215 mOSM/kg	<b>Coagulation</b>	
Lymphocytes	12.0 %			PT(INR)	0.96
Monocytes	7.3 %	<b>Blood gas analysis</b>		APTT	27.6 sec
Basophils	0.0 %	pH	7.48	FDP	<3 μg/mL
Eosinophils	0.3 %			<b>Infection</b>	
RBC	439×10 <sup>4</sup> /μL	HCO <sub>3</sub> <sup>-</sup>	24.6 mEq/L	HBs antigen	(-)
Hemoglobin	13.5 g/dL	B.E.	2.0 mEq/L	HCV antibody	(-)
Hematocrit	35.2 %	anion gap	9.0 mEq/L	STS	(-)
Platelet	23.3×10 <sup>4</sup> /μL				

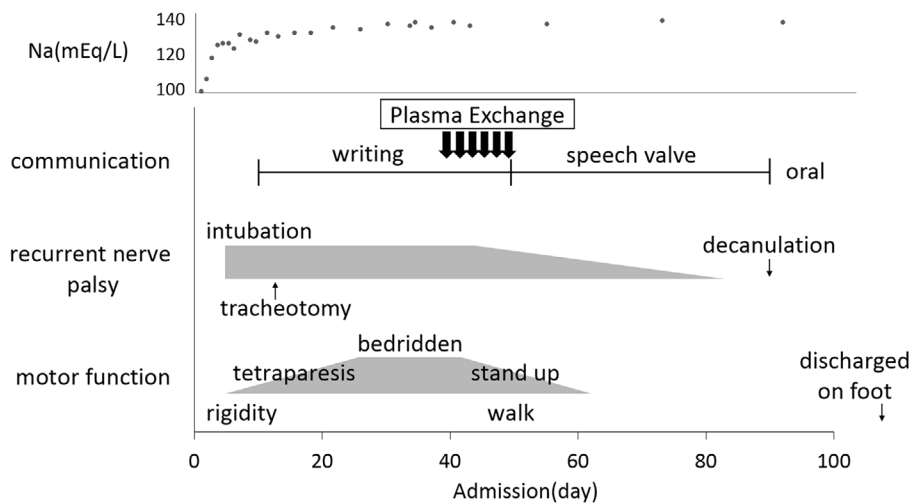
RBC: red blood cell, u-: urinary, OSM: osmolality, UN: urea nitrogen, Na: sodium, K: potassium, Cl: chloride, Cr: creatinine, WBC: white blood cell, TP: total protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, BUN: blood urea nitrogen, TG: triglyceride, LDL: low density lipoprotein, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, pOSM: plasma osmolality, B.E. base excess, IgG/A/M: immunoglobulin G/A/M, CH50: complement hemolytic activity, C3/C4: complement, ANA: anti-nuclear antibody, TSH: thyroid stimulating hormone, hANP: human atrial natriuretic peptide, PRA: plasma renin activity, ACTH: adrenocorticotrophic hormone, AVP: arginine vasopressin, PT(INR): thrombin time (international normalized ratio), APTT: activated partial thromboplastin time, FDP: fibrin and fibrinogen degradation products, HBs: hepatitis B surface, HCV.: anti-hepatitis C, STS: serological test for syphilis

(ECG) showed no evidence of arrhythmia. We suspected that her consciousness disorder was due to severe hyponatremia. Since her serum sodium level had fallen from 135 mEq/L at approximately one month before admission to 108 mEq/L a few days before admission to our hospital, we concluded that her hyponatremia had chronically progressed. We started correcting her serum sodium level with an intravenous infusion of normal saline by calculating the sodium dosage and infusion speed. On the second hospital day, her serum sodium level reached 108 mEq/L. She became alert and we allowed her to ingest meals that contained about 10 g of NaCl. On the third hospital day, her serum sodium level had risen to 120 mEq/L. Because we thought the correction was too rapid, we switched the intravenous drip infusion from normal saline to half saline. However, a few hours later, she was unable to follow our commands. Her serum sodium level was still 120 mEq/L and her serum phosphate level was 1.0 mg/dL. Her serum phosphate level was 2.5 mg/dL on the second day of hospitalization and decreased to 1.9 mg/dL on the morning of the third day. We prescribed sodium phosphate and water-soluble vitamins with saline or half saline to treat the deficiency while supplying few calories. At first, we suspected that her consciousness disturbance was due to delirium or ODS. After her consciousness deteriorated the following day, we performed head CT and brain MRI. We also consulted neurologists, who ruled out ODS based on the diagnostic imaging and physical findings. She became comatose, and rigidity was found in her extremities. A few hours later, we found her snoring, and gradually her oxygen saturation level started to fall. We performed tracheal intubation immediately for airway protection. Electroencephalography (EEG) and lumbar puncture did not help in making a diagnosis. Within

2 days, she became alert and was extubated. We found her having difficulty in expectorating sputum. Laryngoscopy resulted in a diagnosis of recurrent nerve palsy, and tracheotomy was performed. Spastic tetraparesis and deep tendon hyperreflexia were noted, and the Babinski reflex was observed. Her tetraparesis worsened day by day and it soon became difficult for her to stand, move her face, or swallow. The transient consciousness and respiratory disorder might have been due to refeeding syndrome or Wernicke encephalopathy. But we could hardly explain the progressive tetraparesis and recurrent nerve palsy after she became alert. On the 26th day of hospitalization, brain MRI revealed a fresh high signal region in the pons and the bilateral basal ganglia, which led us to make a diagnosis of ODS (Fig. 1). On the 39th day of hospitalization, we started consecutive PE, at a rate of 2-3 sessions per week for total of 6 sessions (Fig. 2). Since her body weight was 55 kg and her Hct value was 33%, her estimated plasma volume was  $55 \times 0.065 \times (1-0.33) = 2.4$  L. We exchanged a total volume of 3,840 mL of fresh frozen plasma (FFP) (approximately one and a half times the volume of her plasma;  $2.4 \times 1.5 = 3.6$  L). Her spastic tetraparesis showed significant improvement after the start of PE therapy, and she was able to stand by herself and walk after the second session of PE. Laryngoscopy revealed improved vocal cord movement. We tried closing the tracheostoma on the 92nd day of hospitalization. The high signals in the pons and bilateral basal ganglia were reduced in size but remained after the completion of PE therapy (Fig. 1). She was able to eat and drink without aspirating, and walked on foot unassisted on the 111th day of hospitalization.



**Figure 1.** A fluid attenuated inversion recovery (FLAIR) sequence of brain MRI. The arrow shows the basal ganglia and pons in a time series.



**Figure 2.** The clinical course.

## Discussion

The laboratory findings on admission, including a serum osmolality of 215 mOsm and a serum sodium level of 108 mEq/L, showed hypoosmotic hyponatremia. The patient's lower limbs were slightly edematous on admission to the emergency department, but her chest X-ray showed a normal cardiac silhouette and no evidence of pleural fluid. A loss of appetite for a few days resulted in a fractional excretion of sodium value of 0.47% and a fractional excretion of urea nitrogen value of 33.9%, which indicated mild hypovolemia. The urinary sodium level was 64 mEq/L, and the urinary chloride level was 88 mEq/L. Both the urinalysis findings and her serum human atrial natriuretic peptide level (32.7 pg/mL) ruled out severe hypovolemia. Hormonal tests revealed the patient was euthyroid. A rapid ACTH test showed no evidence of adrenocortical insufficiency, and a CRH/

TRH/GnRH/GHRH tolerance test ruled out hypopituitarism. The serum AVP level of 2.6 pg/mL was high for an osmolality of 215 mOsm, and we suspected syndrome of inappropriate secretion of antidiuretic hormone (SIADH). No obvious cause of SIADH, such as malignancy, inflammatory disease, or central nervous system disorder was detected other than the physical stress caused by admission, and mental stress prior to admission. Her serum phosphate and potassium levels were slight decreased. An examination to investigate sodium and other electrolyte disorders, led to a diagnosis of hyponatremia due to thiazide diuretics. It is well-known that thiazide diuretics sometimes cause hyponatremia, and that it can happen after taking diuretics for a few years. Some drugs induce hyponatremia when taken with thiazide diuretics (4, 5).

The etiology of ODS is not clear, but it is considered to be an iatrogenic disease that is caused by a rapid rise in the serum level of sodium (1). The damage to the blood-brain

barrier by osmotic change is thought to result from the exposure of the brain to myelinotoxic substances (6, 7). The speed at which the serum sodium level is corrected should be decided carefully when treating chronic hyponatremia; however, it is not unusual for the serum sodium level to differ from the expected values (2).

The re-induction of hyponatremia is reported to be beneficial for preventing ODS due to a rapid correction of hyponatremia (8, 9). Other treatments, such as the administration of TRH, corticosteroids (6, 10), immunoglobulins (11), and PE (3) were suggested by case reports. Minocycline is said to be effective in preventing ODS in the rat models (12). However, there are no proven, effective treatments for ODS. In the present case, it took more than one month to diagnose ODS. In the chronic phase of ODS, we could not expect the same effect of a re-lowering serum sodium level. Since plasma apheresis is known to be effective in treating demyelinating neuropathy (13), we decided to treat our patient using PE. The direct effects of PE on the blood-brain barrier have not been proven; however, her symptoms improved dramatically, immediately after the initiation of PE. The improvement of the nerve cells or neuron system is unlikely to occur with a single PE session. The previous case reports in which PE was shown to be beneficial in the treatment of acute-phase ODS indicate that the improvement of ODS-associated symptoms following PE could be explained by the removal of myelinotoxic substances, which are involved in the pathogenesis of ODS.

On the other hand, in the present case, the introduction of PE in the chronic phase improved her neurological symptoms, suggesting that myelinotoxic substances work not only as an exacerbating factor but also as a suppressor of neural activity. It has been reported that 31% of ODS patients died and that 31% required life-supporting therapy after one year of follow-up (14). There are likely to be cases that are thought to be incurable in which physicians give up treatment after diagnosing ODS. Not all the cases require plasma exchange; however, it could be an effective treatment for chronic ODS.

PE could therefore be a beneficial treatment for chronic ODS.

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

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