Takotsubo Cardiomyopathy in a Patient with Severe Hyponatremia Associated with Syndrome of Inappropriate Antidiuretic Hormone

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Abstract

Although the etiology of Takotsubo cardiomyopathy (stress-induced cardiomyopathy) is unknown, there is a wide variability in the psychological and physical triggers for Takotsubo cardiomyopathy. We report here a case of Takotsubo cardiomyopathy associated with severe hyponatremia.

Key words: cardiomyopathy, hyponatremia, sodium

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Introduction

Takotsubo cardiomyopathy, or stress-induced cardiomyopathy, is characterized by reversible left ventricular apical ballooning associated with emotional or physiological stress, which mimics acute myocardial infarction in the absence of significant coronary artery disease at angiography (1-3). The precise mechanism of Takotsubo cardiomyopathy remains obscure, although its onset is triggered by acute illness or intense emotional or physical stress (4, 5). Some investigators have reported Takotsubo cardiomyopathy associated with hyponatremia (6-8). We report here a case of Takotsubo cardiomyopathy in severe hyponatremia associated with the syndrome of inappropriate antidiuretic hormone (SIADH).

Case Report

An 82-year-old Japanese man was undergoing regular follow-up by his family doctor for chronic alcoholism, epilepsy, and gastrectomy performed for gastric cancer. He had been admitted to our hospital because of Mallory-Weiss syndrome and hyponatremia approximately 6 months previously. At that time, based on his test data, he was diagnosed with SIADH; serum sodium level, 110 mEq/L; serum osmo-

lality, 240 mOsm/kg; urine osmolality, 518 mOsm/kg; urine sodium level, 87 mEq/L; arginine vasopressin, 0.6 pg/mL. His electrocardiogram (ECG) was normal (Fig. 1A) and he had no signs or symptoms of heart failure or heart disease. Four days after treatment for hyponatremia with food and fluid restriction (total oral intake, 500 mL per day) and saline infusion (500 mL/day), his serum sodium level was increased from 110 mEq/L to 122 mEq/L, and saline infusion was stopped and food intake was gradually increased. He was discharged with a serum sodium level of 134 mEq/L about 2 weeks after admission.

After discharge, he was admitted to a psychiatric hospital for hallucinations and violent behavior. His medication profile included phenytoin, 200 mg; flunitrazepam, 1 mg; trazodone hydrochloride, 50 mg; famotidine, 20 mg, each once daily. About one month after admission to the psychiatric hospital, an echocardiography was performed in our hospital because of sinus bradycardia and it showed normal wall motion of left ventricle. Subsequently, he was transferred to our hospital following complaints of dyspnea and vomiting about three months after admission to the psychiatric hospital.

On examination, his heart rate was 80 beats/min and blood pressure was 90/60 mmHg. His consciousness level corresponded to Japan Coma Scale 100, and no apparent neurological deficit was observed. Although a brain CT and

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Figure 1. Electrocardiography (ECG) before and after admission. A: ECG on previous admission; ECG showed sinus rhythm, flat T wave in aV_L . B: ECG on admission: ECG showed left axis deviation and ST-segment elevation in II, III, aV_F , and V_{2-6} . C: ECG on the day after admission: ECG showed negative T wave in II, III, aV_F , and V_{2-6} .

Figure 2. Brain computed tomography (CT) and magnetic resonance image (MRI) on admission. Brain CT showed no acute cerebral infarction and bleeding, and mild atrophy of bilateral anterior lobes was seen (A). Brain MRI showed mild atrophy of bilateral anterior lobes and severe atrophy of right (B) and left (C) bilateral mammillary bodies (arrows) were seen.

MRI showed no acute cerebral infarction or bleeding, mild atrophy of the bilateral anterior lobes and severe atrophy of bilateral mammillary bodies were observed (Fig. 2). His chest radiography showed no abnormal findings except for pleural calcification. The initial ECG showed a sinus rhythm and ST-segment elevation in V_{1-5} (Fig. 1B). His serum sodium level was 104 mEq/L; uric acid, 2.2 mg/dL; blood urea nitrogen, 7.4 mg/dL; creatinine, 0.53 mg/dL; serum osmolality, 246 mOsm/kg; urinary osmolality, 169 mOsm/kg; urinary sodium, 23 mEq/L. The serum level of creatine kinase was normal but his serum cardiac troponin I was 2.193 ng/mL (normal, <0.04 ng/mL), and the serum level of brain natriuretic peptide (BNP) was 1025.6 pg/mL (Table 1); furthermore, laboratory data showed normal thyroid and adrenal function, but serum levels of norepinephrine and dopamine were increased (Table 1). His echocardiography showed akinesis of the left ventricular apex (Fig. 3A and B), and an emergent cardiac catheterization was performed. Coronary angiography showed no significant coronary

stenosis, although left ventriculography demonstrated akinesis of the left ventricular apex (Fig. 4A, B). Based on these data, the patient was diagnosed with Takotsubo cardiomyopathy. He was immediately treated with intravenous saline infusion with total parenteral nutrition (total fluid of 1,500 mL/day and total NaCl infusion of 200 mEq/day) to correct his serum sodium level with treatment for heart failure due to Takotsubo cardiomyopathy with intravenous infusion of 20 mg furosemide per day, and a serum sodium level was increased as follows: 120 mEq/L, 2 days after admission; 131 mEq/L, 5 days after admission.

The following day, an ECG showed a negative T wave in V_{2-6} (Fig. 1C). His condition had improved, and two weeks after admission, echocardiography showed normal kinesis of the left ventricular apex (Fig. 3C, D). About 1 month after the admission, he was discharged with a serum sodium level of 136 mEq/L and a serum level of BNP of 135 pg/mL.

Table 1. Laboratory Data

WBC: 6710 / μ L	Na: 105 mEq/L	ALP: 690 IU/L	BNP: 1025.6pg/mL
RBC: 310 $\times$ 10 ⁴ / μ L	K: 4.7 mEq/L	γ -GTP: 81 IU/L	E: 0.02 ng/mL (0.0-0.1)
Hb: 9.3 g/dL	Cl: 78 mEq/L	CK: 60 IU/L	NE: 1.25 ng/mL (0.1-0.5)
Hct: 25.3%	P: 2.3 mg/dL	CK-MB: IU/L	DA: 1.80 ng/mL (0.00-0.03)
Plt: 5.8 $\times$ 10 ⁴ / μ L	Ca : 6.9 mg/dL	AMY: 90 IU/L	Cortizol 20.8 mg/dL (4.5-21.1)
PT (INR) 1.10	BUN : 7.4 mg/dL	Ch-E: 157 IU/L	TSH: 1.0714 μ IU
	Cre: 0.53 mg/dL	UA: 2.2 mg/dL	free T4: 1.07 ng/dL
HBsAg(-)	TP : 4.9g/dL	Glu: 107 mg/dL	free T3: 0.63 pg/mL
HCVAb(-)	Alb: 2.5 g/dL	LDL-C: 76 mg/dL	Serum Osm 246 mOsm/kg
TPHA(-)	T bil 0.5: mg/dL	HDL-C: 48 mg/dL	Urine Osm 169 mOsm/kg
RPR (-)	AST: 32 IU/L	TG: 49 mg/dL	Urine Na 23mEq/L
	ALT: 19 IU/L	CRP: 6.11 mg/dL	ADH 0.8 pg/mL (0.3-4.2)
	LDH: 167 IU/L	Troponin I: 2.193ng/mL	

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; PLT, platelet
 BUN, blood urea nitrogen; Cr, creatinine; TP, total protein; Alb, albumin; T bil, total bilirubin,
 AST, aspartate aminotransferase; ALT, alanine aminotransferase
 LDH, lactate dehydrogenase; ALP, alkaline phosphatase, ; γ -GTP, γ -glutamyltransferase
 CK, creatine kinase; AMY, amylase; Ch-E, cholinesterase; UA, uric acid
 Glu, glucose; LDL-C, low-density lipoprotein cholesterol
 HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; CRP, c-reactive protein;
 BNP, brain natriuretic peptide; E, epinephrine; NE, norepinephrine; DA, dopamine,
 TSH, thyroid stimulating hormone; Osm, osmolality; ADH, antidiuretic hormone

Discussion

Hyponatremia is the most commonly observed electrolyte imbalance in hospitalized patients, and a majority of patients with hyponatremia are asymptomatic and do not require immediate correction (9, 10). In contrast, symptomatic hyponatremia is a medical emergency requiring rapid correction to prevent worsening of brain edema, and is associated with increased morbidity and mortality; however symptomatic hyponatremia is frequently under-recognized and untreated (9, 10). Only four cases have reported Takotsubo cardiomyopathy associated with hyponatremia without adrenal insufficiency and hypothyroidism (Table 2) (6-8). All of these cases had severe hyponatremia (Na <125 mEq/L). Severe hyponatremia, if developing rapidly (within 48 hours), involves critical symptoms, such as confusion, unconsciousness, grand mal seizures, and even death. In the present case, Takotsubo cardiomyopathy occurred at the serum sodium level of 105 mEq/L, although it did not occur at the serum sodium level of 110 mEq/L on previous admission. Thus, the severity of hyponatremia seems important for the occurrence of Takotsubo cardiomyopathy, although according to previous reports the threshold serum sodium levels at which it occurs may be different among patients (Table 2).

Two of these 4 published cases developed Takotsubo cardiomyopathy following a hyponatremic seizure (6, 7). Seizure is also associated with Takotsubo cardiomyopathy (11), and these studies suggest that seizure induces a catecholamine storm or sympathetic surge that provokes Takotsubo cardiomyopathy. The patient in this case had confusion without seizure at the time of present admission because he was on phenytoin medication for epilepsy. Thus, in the pre-

sent case, seizure was not a direct trigger of Takotsubo cardiomyopathy. AbouEzzeddine and Prasad (8) reported 2 cases of Takotsubo cardiomyopathy triggered by hyponatremia without epilepsy. They suggested that Takotsubo cardiomyopathy occurred as a direct consequence of hyponatremia. In the present case, we demonstrated high serum levels of dopamine and norepinephrine. Although the precise mechanism of Takotsubo cardiomyopathy has not been determined, an acute catecholamine toxicity of the myocardium has been believed to be one of the causes (5). Norepinephrine is a sympathetic neurotransmitter and dopamine is its precursor. These facts suggest that excessive catecholamine release from sympathetic nerves may provoke Takotsubo cardiomyopathy with severe hyponatremia, although severe hyponatremia did not induce seizure. However, the mechanism of excessive catecholamine release by severe hyponatremia is still unknown.

There are several causes of hyponatremia and the most common causes in adults are therapy with thiazides, the postoperative state and other causes of SIADH, polydipsia in psychiatric patients, dehydration, hypothyroidism, adrenal insufficiency, and volume overload related to heart failure, nephritic syndrome, and cirrhosis (12). Considering the 4 previous reports, hyponatremia in Takotsubo cardiomyopathy was attributed to SIADH (n=2), diuretics (n=1), and unknown causes (n=1).

Although the causes of SIADH are myriad, they include disorders of the central nervous system and antipsychotic or psychotropic drugs. Moreover, the 2 previously reported cases associated with SIADH had disorders of the central nervous system or psychiatric disorders, and the one previously reported case with unknown cause for hyponatremia had schizophrenia. This suggests that disorders of the central

Figure 3. Echocardiography (UCG) on admission and about 2 weeks after admission. UCG demonstrated akinesis of apex of the left ventricle (A, end-diastolic phase; B, end-systolic phase) on admission and showed recovered apical wall motion of the left ventricle 2 weeks after admission (C, end-diastolic phase; D, end-systolic phase).

nervous system and/or psychiatric disorders, in addition to severe hyponatremia, play important roles in the catecholamine release.

In the present case, the patient was on antipsychotic drugs for chronic alcoholism. These antipsychotic drugs may have progressed the severity of hyponatremia which is related to Takotsubo cardiomyopathy. Furthermore, his MRI showed atrophy of the bilateral mammillary bodies with mild frontal lobe atrophy. Classically, acute thiamine deficiency-associated Wernicke's encephalopathy (WE) is marked neuropathologically by lesions of periventricular nuclei, hypothalamic nuclei, tectal plate, and thalamus, which are caused

by thiamine (vitamin B1) deficiency. Acute WE when left untreated or if treated incompletely with thiamine or too late can lead to profound, debilitating global amnesia that is a marker for Korsakoff syndrome. In this later phase, targeted structures, notably the mammillary bodies, become atrophic (13, 14). To date, only one report has demonstrated a relationship between SIADH and WE (15). Thus, Korsakoff syndrome may be related to the cause of SIADH and the mechanism of occurrence of Takotsubo cardiomyopathy with severe hyponatremia in the present case. Although the present case had two important factors for thiamine deficiency, i.e., chronic alcoholism and gastrectomy, we did not mea-

Figure 4. Coronary angiography (CAG) and Left ventriculography (LVG) on admission. CAG showed normal right (A) and left (B) coronary arteries. LVG demonstrated akinesis of the apex of the left ventricle (C, end-diastolic phase; D, end-systolic phase) on admission.

Table 2. Reports of Takotsubo Cardiomyopathy with Hyponatremia

	Age	Sex	Disease	Na (mEq/L)	Association with Seizure	Cause of Hyponatremia	Ref
1	69	F	multiple sclerosis	109	Y	SIADH	6
2	63	F	schizophrenia	110	Y	not determined	7
3	76	F	hypertension, diabetes	120	N	Diuretics	8
4	57	F	bipolar disorder	111	N	SIADH	8
5	82	M	chronic alcoholism, epilepsy	105	N	SIADH and Vomit	Our case

Y, yes; N, No; SIADH, syndrome inappropriate antidiuretic hormone

sure the thiamine level because the patient had a vitamin infusion immediately before he was transferred to our hospital. However, his psychiatric problems improved and serum sodium level was easily maintained at a normal level after treatment with thiamine in addition to the sodium supplementation.

In the present case, admission to a psychiatric hospital did not seem to be a major trigger for occurrence of Takotsubo cardiomyopathy although it may influence it in part because echocardiography showed normal wall motion of the left ventricle about one month after admission to the psychiatric hospital, and there was no episode as a stress event for him before the occurrence of Takotsubo cardiomyopathy. More-

over, we have no evidence of Korsakoff syndrome itself as a trigger for the induction of Takotsubo cardiomyopathy, and there is no report on it to date. Further study seems necessary to evaluate this possibility.

In conclusion, we should consider the importance of severe hyponatremia as a stressor for Takotsubo cardiomyopathy, especially in association with diseases of the central nervous system and/or psychiatric disorder.

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

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