Status Epilepticus Related Takotsubo Syndrome – A Case Report

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Abstract

Purpose: Takotsubo syndrome (TTS) is characterized angiographically by transient left ventricular systolic dysfunction sparing the basal segments of the left ventricle and absence of obstructive coronary artery disease. Epileptic seizures as triggering events for TTS are uncommon, having only been described in approximately 100 previous cases

Case report: A 64-year-old woman with a history of recent stroke-related seizures was admitted for an acute onset of right hemiparesis with dull response. Neurological examination revealed a forced deviation of the eyeballs to the left side and quadriplegia. No large intracranial artery occlusion was disclosed through computed tomography angiography, but an acute infarction at the right corona radiata was identified through magnetic resonance imaging. Electroencephalography showed frequent spike-and-wave complexes over the right cerebral hemisphere indicating subtle status epilepticus. Her consciousness deteriorated to a stuporous state, and her eyeballs were forced deviated to the right side with persistent twitching of the right limbs 10 hours later. The convulsive status epilepticus (CSE) subsided after intravenous infusion of midazolam. However, atrial flutter with inverted T-wave and elevated high-sensitivity troponin I were observed 12 hours after CSE. Arrhythmia was soon alleviated through appropriate treatment. A further coronary angiography did not show significant coronary artery stenosis but indicated that the midsection and the apex of the left ventricle ballooned out during systole as the base contracted normally, indicating a Takotsubo syndrome.

Conclusion: Physicians need to monitor unusual arrhythmias, particularly atrial and ventricular arrhythmias, for the possibility of TTS in patients with epileptic seizure.

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INTRODUCTION

Takotsubo syndrome (TTS) or Takotsubo cardiomyopathy - also described as stress cardiomyopathy, apical ballooning syndrome, or broken heart syndrome - is regarded as an acute coronary syndrome in the absence of obstructive coronary artery disease. TTS is characterized angiographically by transient left ventricular

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systolic dysfunction sparing the basal segments of the left ventricle[1]. The incidence of TTS is estimated to be 1% to 2% of patients presenting with an acute myocardial infarction[2]. Central nervous system (CNS) diseases may cause some cardiac abnormalities including TTS. The mechanism of TTS induced by CNS disease is most likely to involves catecholamine stress following fear, pain, or anxiety[3]. Numerous CNS diseases, including subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, epilepsy, encephalitis or meningitis, brain injury, and posterior reversible encephalopathy syndrome, might trigger TTS[3]. Seizure has been reported to be the second or third most common neurologic trigger of TTS[3,4]. Epileptic seizures as triggering events for TTS are uncommon, having only been described in approximately 100 cases in Finsterer's and Belcour's reports[3,5,6]. A nationwide population-based study conducted by Desai et al. reported that 1 in every 1000 epilepsy-related hospitalizations was associated with secondary TTS[7]. We present a patient who developed TTS presenting as atrial flutter 12 hours after mixed subtle and convulsive status epilepticus (CSE).

CASE REPORT

A 64-year-old woman with a history of hypertension, hyperlipidemia, and progressive impairment of both cognitive function and daily activities for the preceding 2 years experienced an ischemic stroke at the right corona radiata with left hemiplegia 4 months prior to this admission. During previous hospitalization, a survey of dementia, including autoimmune and paraneoplastic antibodies, detected an elevation of anti-Yo antibody in the cerebrospinal fluid. However, no any malignant lesions were found either through a survey of tumor markers or whole-body computed tomography (CT). She had a stroke-related focal seizure presenting as twitching left limbs during previous hospitalization and had received lacosamide 200 mg daily for seizure control. She was discharged to the nursing home with the sequelae of left hemiplegia and dementia. On this occasion, she was admitted to the intensive care unit due to an acute onset of right hemiparesis with speechless and dull response. Her blood pressure was 156/78 mmHg with a regular heart rate of 118 beats/min. A neurological examination revealed a Glasgow Coma Scale score of E4V1M5-6, forced deviation of the eyeballs to the left side, and a quadriplegia. The muscle power of her right limbs was grade 2/5 (Medical Research Council of Great Britain), which was reported to be new-onset weakness; as a sequelae of previous stroke, her left limbs were grade 1/5. An electrocardiogram (ECG) indicated sinus tachycardia. A chest X-ray was normal. Brain CT indicated leukoaraiosis and multiple old lacunar infarcts mainly at the regions of the right basal ganglion and corona radiata. Brain CT angiography did not indicate large intracranial artery occlusion but revealed a severe focal stenosis at the left distal internal carotid artery and a mild atherosclerosis of the bilateral middle cerebral arteries. Emergent electroencephalography (EEG) identified frequent spike-and-wave complexes over the right cerebral hemisphere (Figure 1). Under a highly suspicion of subtle generalized convulsive status epilepticus, or subtle status epilepticus (SSE), we prescribed intravenous depakine 400 mg every

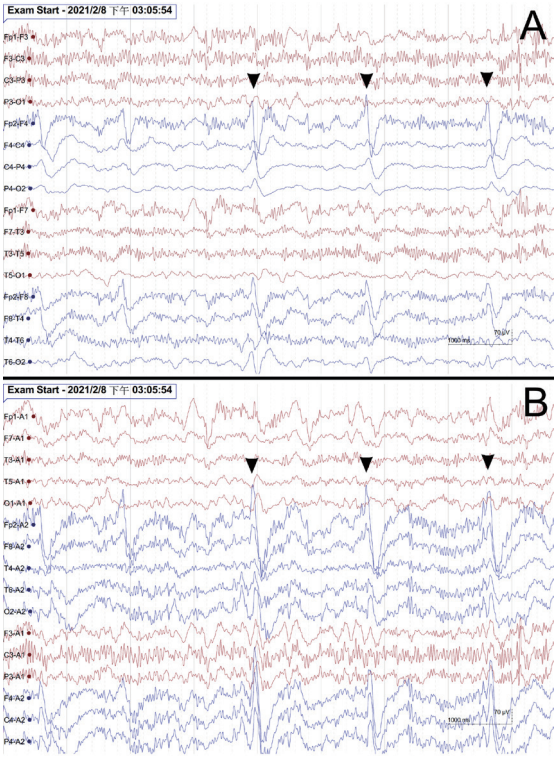

Figure 1. Electroencephalography showing frequent spike-and-wave complexes over the right cerebral hemisphere (arrowheads) in bipolar montage (A) and monopolar montage (B).

8 hours for seizure control.

Subsequently, her consciousness deteriorated to a stuporous state with persistent twitching of the right limbs and forced deviation of the eyeballs to the right side 10 hours after admission, which could not be alleviated by intravenous lorazepam and a further loading dose of depakine. A CSE with an epileptic focus located at the left hemisphere was suspected. Consequently, we added a loading dose of intravenous midazolam 2 mg/kg, followed by a continuous infusion of midazolam 0.2 mg/kg/hour. The CSE subsided 1 hour later. However, her systolic blood pressure dropped to 70 mmHg 40 minutes after the limbs stopped twitching. We discontinued the intravenous midazolam infusion, and the systolic blood pressure gradually returned to 90 mmHg. The next day, brain magnetic resonance imaging revealed an acute new infarction at the right corona radiata (Figure 2).

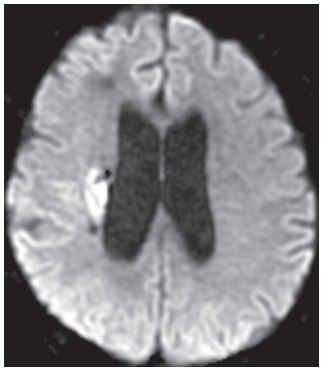

Figure 2. Diffusion-weighted magnetic resonance image showing an acute infarct at the right corona radiata.

Atrial flutter with an increased heart rate of up to 142 beats/min and abnormally inverted T-wave was observed 12 hours after onset of right-limbs twitching (Figure 3). We immediately administered defibrillation therapy with intravenous amiodarone 300 mg. The heart rate soon returned to a normal sinus rhythm. Immediate laboratory studies revealed elevated levels of creatine kinase (CK; 954 U/L; reference level: 30–223 U/L), CK-MB (7.3 ng/mL; reference level: 0.6–6.3 ng/mL), and high-sensitivity troponin I (hs-troponin I; 14,425 pg/mL; 99th percentile upper reference limit: <17.5 pg/mL). Echocardiography showed hypokinesia of the left ventricle at the middle septum and the apex with an ejection fraction of 44% (Figure 4A and B). Ischemic heart disease or TTS was suspected. Further emergent coronary angiography did not show significant coronary artery stenosis but demonstrated that the midsection and the apex of the left ventricle ballooned out (apical ballooning) during systole while the base of the left ventricle contracted normally (Figure 4C and D). TTS was confirmed. The level of hs-troponin I decreased to 6170 pg/mL 15 hours later. However, the patient's consciousness and the muscle strength of the right limbs did not improve thereafter. A follow-up EEG on day 10 revealed diffuse slow waves over bilateral cerebral hemispheres without epileptiform discharge.

Due to the patient having been rendered totally dependent in activities of daily living by her first stroke

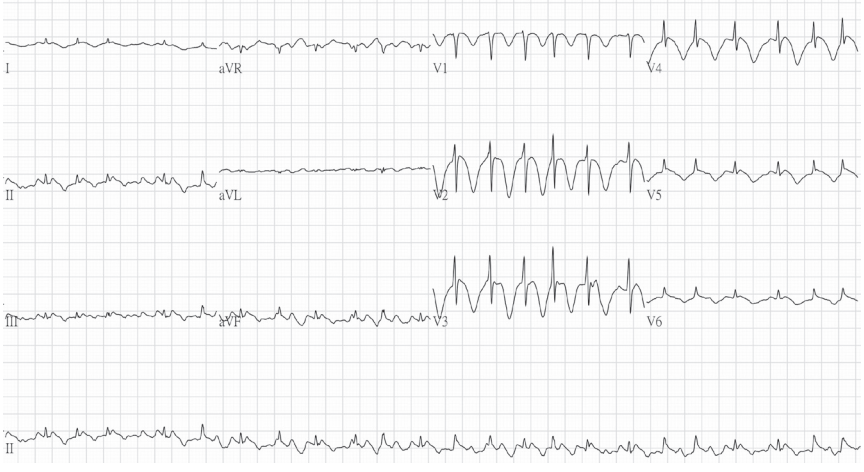

Figure 3. Electrocardiogram showing atrial flutter with variable atrioventricular block and marked inverted T-wave.

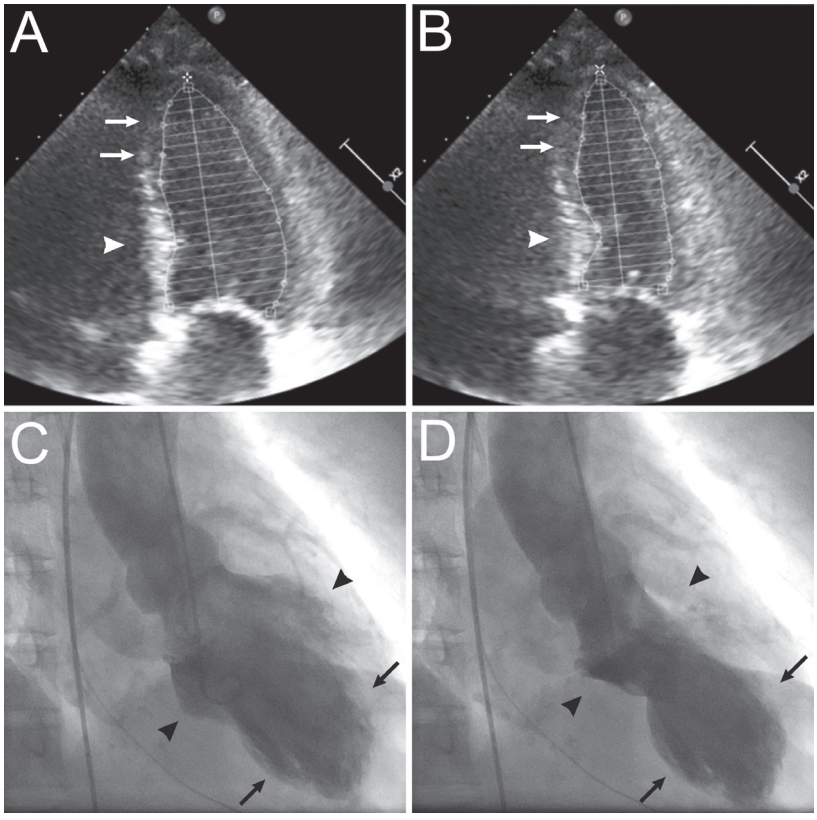

Figure 4. (A and B) Echocardiography with apical four chambers view during diastolic (A) and systolic phase (B) showing hypokinesis of the middle and apical septum (white arrows) with preserved systolic function of the basal septum of the left ventricle (white arrowheads). (C and D) Left ventriculogram during diastolic (C) and systolic phase (D) showing akinesis of the mid-segment and apex (black arrows) with preserved systolic function of the basal segment of the left ventricle (black arrowheads).

coupled with the prolonged disturbance of consciousness with quadriplegia during this hospitalization, her family members decided to continue conservative treatment and refused a follow-up coronary angiographic study. Her endotracheal tube was extubated on day 32, and she was transferred to hospice care on day 45; and she was discharged to a nursing home 90 days after admission.

DISCUSSION

This patient presented to the emergency department on the second occasion with dull response and right-limbs weakness, and her eyeballs exhibited forced deviation to the left side mimicking an acute stroke involving the left hemisphere. Seizure disorder, which has been reported to be the most common cause of stroke mimic[8,9], was suspected after excluding an intracranial large-artery occlusion through the emergent CT angiography together with a history of recent stroke with poststroke epilepsy. The frequent spike-and-wave complexes over the right cerebral hemisphere identified by EEG study could cause a deviation of the eyeballs to the left side. The right limbs weakness might be more appropriately regarded as a quadriplegia during a state of subtle generalized convulsive status epilepticus (or subtle status epilepticus; SSE), which is a subtype of nonconvulsive status epilepticus[10,11]. The subsequent occurrence of CSE with eyeballs deviation to the right side and right limbs twitching 10 hours later was soon controlled through anticonvulsant medications. Although EEG study was not repeated during this stage, we presumed another epileptic focus located at the left cerebral hemisphere, which was contralateral to the right

hemisphere disclosed by the initial EEG study, resulting in right-sided eyeball deviation and right limbs twitching. The acute cerebral infarction located at the same region of the previous stroke was possibly related to an excessive drop in the blood pressure during treatment for CSE. Finally, she developed TTS presenting as atrial flutter and elevated hs-troponin I 12 hours after CSE onset.

TTS was originally named in 1990 by Sato et al., who observed in Japanese patients an unusual shape change of the left ventricle of the heart resembling an octopus-trapping pot with a round bottom and narrow neck[12]. TTS is characteristically triggered by severe emotional or physical stress, which plays a pathogenic role in increasing sympathetic activity, leading to myocardial perfusion abnormalities and ventricular dysfunction[1]. The diagnosis of TTS is mainly based on the Mayo Clinic criteria including: 1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegments with or without apical involvement; 2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; 3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and 4) absence of pheochromocytoma or myocarditis[2]. Sympathetic hyperactivity can cause cardiac stunning and contractile dysfunction[13]. Myocyte injury occurs due to the decreased viability of myocytes through overloaded cyclic AMP-mediated calcium and increased availability of oxygen-derived free radicals[14]. During severe emotional or physical stress, the apical segments of the myocardium exhibited enhanced responsiveness to sympathetic stimulation, thus rendering the apex more vulnerable to sudden surges in catecholamine levels[15]. Accordingly, a persistently dilated left ventricle at the apex during systole and diastole results in the typical cardiac shape of apical ballooning in angiographic study, which resembles a takotsubo, or octopus-trapping pot.

Among seizure disorders, general-onset tonic-clonic seizures followed by status epilepticus and focal onset impaired awareness seizures have been found to be more frequently associated with TTS[5]. The all-cause in-hospital mortality rate has also been reported to be higher in the epilepsy-TTS group compared with the epilepsy-non-TTS group[7], and the epilepsy-TTS group had significantly higher rates of arrhythmia, stroke, cardiogenic shock, cardiac arrest, venous thromboembolism, and respiratory failure compared with the epilepsy-non-TTS group. Given that treatment of TTS significantly improves patient outcomes, the recognition and identification of TTS after patients experience a seizure is crucial. Although TTS has been speculated to be a mechanism possibly related to sudden unexpected death in epilepsy, Finsterer et al. found that only 3% of patients who experience seizure-triggered TTS had a fatal outcome[5].

Compared with a single episode of seizure, TTS tends to occur more after CSE, which is defined as 5 minutes or more of continuous seizures, or two or more discrete seizures between which the recovery of consciousness is incomplete.16 A prospective study conducted by Belcour et al. found that the overall prevalence of TTS after CSE ranged from 34% to 62%[6]. However, only 32 patients with status epilepticus-related TTS were reported in Nadal's review in 2019, with the majority of seizures categorized as CSE[17].

Typical clinical features of TTS are chest pain and shortness of breath with T-wave or ST-segment abnormalities in ECG mimicking a myocardial infarction[4,6]. Elevated cardiac biomarkers, such as troponin, CK, and CK-MB, can be observed in TTS. However, studies have suggested that the extent of cardiac enzyme elevation is mostly minor[18,19]. The abnormally high level of hs-troponin I observed in our patient was unusual. The elevation of cardiac enzymes during acute stroke is a well-known phenomenon and is an independent factor for unfavorable outcomes[20,21]. Causes of such high level of hs-troponin I in our patient might be a combination of nonconvulsive and CSE along with concurrent acute ischemic stroke. Ventricular arrhythmia, atrial fibrillation, and sinus-node dysfunction have been observed in TTS[22]. The mechanisms of dysrhythmia in TTS include coronary artery vasospasm, microcirculatory dysfunction and transient obstruction of the left ventricular outflow tract[23]. A review conducted by Jesel et al. reported that newly diagnosed atrial arrhythmia (atrial fibrillation and atrial flutter) was observed in 25% of patients with TTS and was associated with poorer short- and long-term prognoses[24]. The most common type of cardiac dysrhythmia observed in patients with epileptic seizure is sinus tachycardia, which accounts for 90% of peri-ictal dysrhythmia. Atrial arrhythmia is a rare peri-ictal phenomenon that complicates seizure disorder[25,26].

Physicians need to monitor any type of arrhythmia, particularly atrial and ventricular arrhythmias, in patients with epileptic seizure for the possibility of TTS.

Most cases of the TTS are reversible, and the function of the left ventricle recovers gradually within weeks to months; however, fatal complications occur in some patients.18 We were unable to determine whether the cardiac function of this patients was improved through follow-up cardiac catheterization or echocardiography due to the decision favoring conservative treatment by the family members. The cause of a prolonged impaired consciousness, even with the disappearance of epileptiform discharge after appropriate treatment, was suspected to be due to a preceding progressive dementia from possible anti-Yo antibody-related paraneoplastic encephalitis, superimposed a hypoxic change of the brain from mixed subtle and convulsive status epilepticus. In the present report, our aim was to increase awareness of the possible occurrence of TTS after status epilepticus. Proper diagnosis and treatment of TTS are critical to avoid an unfavorable outcomes.

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