

Case Report

# Acute encephalopathy with biphasic seizures and late reduced diffusion accompanied by Takotsubo cardiomyopathy

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## Abstract

**Background:** Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is characterized by biphasic seizures and impaired consciousness. Takotsubo cardiomyopathy (TTC), which is typically triggered by psychological or physical stress, is characterized by transient myocardial dysfunction affecting the left ventricular apex. Recent reports have suggested that seizures can also trigger TTC. However, no cases of TTC accompanied by AESD have been reported.

**Patient:** A previously healthy 4-year-old girl was brought to a hospital with first-time febrile generalized tonic-clonic convulsions, which lasted approximately 40 min. After the seizure resolved, she was intubated due to respiratory deterioration. On the next day, her cardiac function deteriorated, and echocardiography revealed systolic apical ballooning of the left ventricle accompanied by hyperkinesis of the basal wall, which are typical in patients with TTC. Her condition gradually improved, and catecholamine support was tapered. However, 6 days after admission, she experienced a cluster of brief convulsions. Ten days after admission, head MRI revealed lesions with reduced diffusion throughout the cortex, except in the occipital lobe, as well as perirolandic sparing. Follow-up MRI 35 days after onset revealed whole-brain atrophy, following which she developed severe cognitive dysfunction.

**Conclusions:** Our patient developed TTC accompanied by features of AESD. Our findings may thus provide insight into the development of TTC and prompt further studies regarding the relationship between prolonged seizures and TTC.

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**Keywords:** Catecholamine; Creatine kinase; Status epilepticus; Takotsubo syndrome; Troponin-T; N-terminal pro-brain natriuretic peptide; Stress

## 1. Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is characterized by biphasic seizures and impaired consciousness. After several days, secondary seizures are followed by reduced diffusion in the cortical and subcortical white matter on magnetic

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resonance imaging (MRI) [1–3]. Although viral infection represents the primary etiology of AESD [1], several cases associated with bacterial infection have also been reported [2,3].

Takotsubo cardiomyopathy (TTC), which is typically triggered by psychological or physical stress, is characterized by transient myocardial dysfunction affecting the left ventricular apex [4,5]. Symptoms of TTC usually resolve within a few weeks in most cases. Creatine kinase (CK), troponin, and N-terminal pro-brain natriuretic peptide (NTproBNP) levels may be elevated in patients with TTC. Furthermore, initial ST elevation can be observed via electrocardiography (ECG) in patients with TTC, dramatically shifting to negative T-waves as the condition progresses [4]. However, there are no definitive diagnostic criteria for TTC in children, likely due to the rarity of the condition and coronary heart disease in general among children.

While several recent reports have suggested that TTC can be triggered by seizures [4–6], no cases of AESD accompanied by TTC have been reported. Here, we discuss a rare case in which a 4-year-old girl developed TTC accompanied by features of AESD.

## 2. Case report

A previously healthy 4-year-old girl was brought to a previous hospital with first-time febrile generalized

tonic-clonic convulsions, which lasted approximately 40 min. Initial examination revealed hemoptysis originating from the nose and mouth, while venous blood gas analysis revealed severe acidosis (pH: 6.726, pCO<sub>2</sub>: 204.0 mmHg, lactate: 26 mg/dL). Although the seizure resolved following the administration of intravenous midazolam and thiopental, she was intubated due to respiratory deterioration. Following intravenous administration of fosphenytoin (22.5 mg/kg), she was admitted to the intensive care unit, where she received a continuous infusion of midazolam and remained on mechanical ventilation. Head computed tomography (CT) revealed slight brain edema. On the next day, she developed hemodynamic instability (heart rate (HR): 143 bpm; arterial blood pressure (BP): 77/59 mmHg), and her cardiac function deteriorated (ejection fraction (EF) (Simpson method): 34% as determined via echocardiography). As myocarditis was suspected, she was transferred to our hospital under catecholamine support (dopamine: 3 µg/kg/min, dobutamine: 3 µg/kg/min, adrenaline: 0.15 µg/kg/min).

Upon admission, she exhibited tachycardia (HR: 172 bpm) without abnormal BP or dilation of the pupils. Echocardiography revealed a left ventricular EF of 47% (Simpson method), which was accompanied by apical ballooning and hypercontractility of the basal portion (Fig. 1). Inverse T waves (V1–V6) were observed on electroencephalography (ECG) (We confirmed that inverse

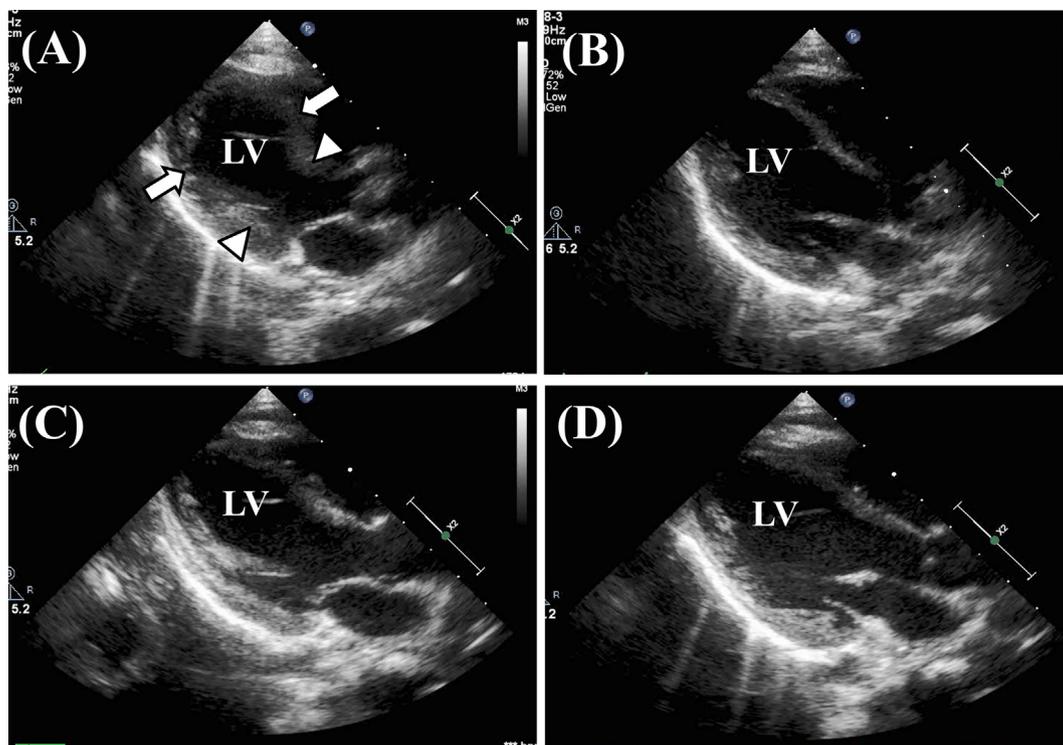


Fig. 1. Echocardiography results during systole (A) and diastole (B). Parasternal long-axis views show systolic apical ballooning of the left ventricle (LV) (white arrow) accompanied by hyperkinesis of the basal wall (white arrowhead), relative to diastole. Improvements in basal hyperkinesis and apical ballooning were observed the next day (systole (C) and diastole (D)).

T waves (V4–V6) had improved following discharge). Laboratory testing revealed abnormal cardiac enzymes (CK: 428 U/L, normal range: 46–230 U/L; troponin-I: 4.59 ng/mL, normal range:  $\leq 0.04$  ng/mL; and NTproBNP: 8669 pg/mL, normal range:  $\leq 125$  pg/mL). Therefore, she was diagnosed with TTC.

Catecholamine support was continued (adrenaline: 0.05  $\mu\text{g}/\text{kg}/\text{min}$ , milrinone: 0.5  $\mu\text{g}/\text{kg}/\text{min}$ ), and mechanical ventilation with high positive end-expiratory pressure was required due to pulmonary edema. As we could not perform a lumbar puncture due to hemodynamic instability, vancomycin (60 mg/kg/day) and acyclovir (30 mg/kg/day) were administered in addition to cefotaxime (300 mg/kg/day). Continuous electroencephalogram (EEG) monitoring was performed, and the patient was started on levetiracetam (60 mg/kg/day),

which was gradually tapered. Fortunately, her hemodynamic status gradually improved, and catecholamine support was discontinued the next day. Echocardiography revealed an improvement in cardiac function (Fig. 1). However, 6 days after admission, she experienced a cluster of brief convulsions, during which continuous EEG monitoring revealed diffuse, rhythmic, high-voltage slow activity. Intravenous midazolam was administered for seizure control. A single-dose of phenobarbital (10 mg/kg) was also administered, following which no seizures occurred. As blood cultures obtained at the previous hospital were negative, cefotaxime and vancomycin were discontinued 7 days after admission. Laboratory data revealed a dramatic improvement in cardiac enzymes (CK: 60 U/L, troponin-I: 0.05 ng/mL, and NTproBNP: 1118 pg/mL) on the same day. Eight

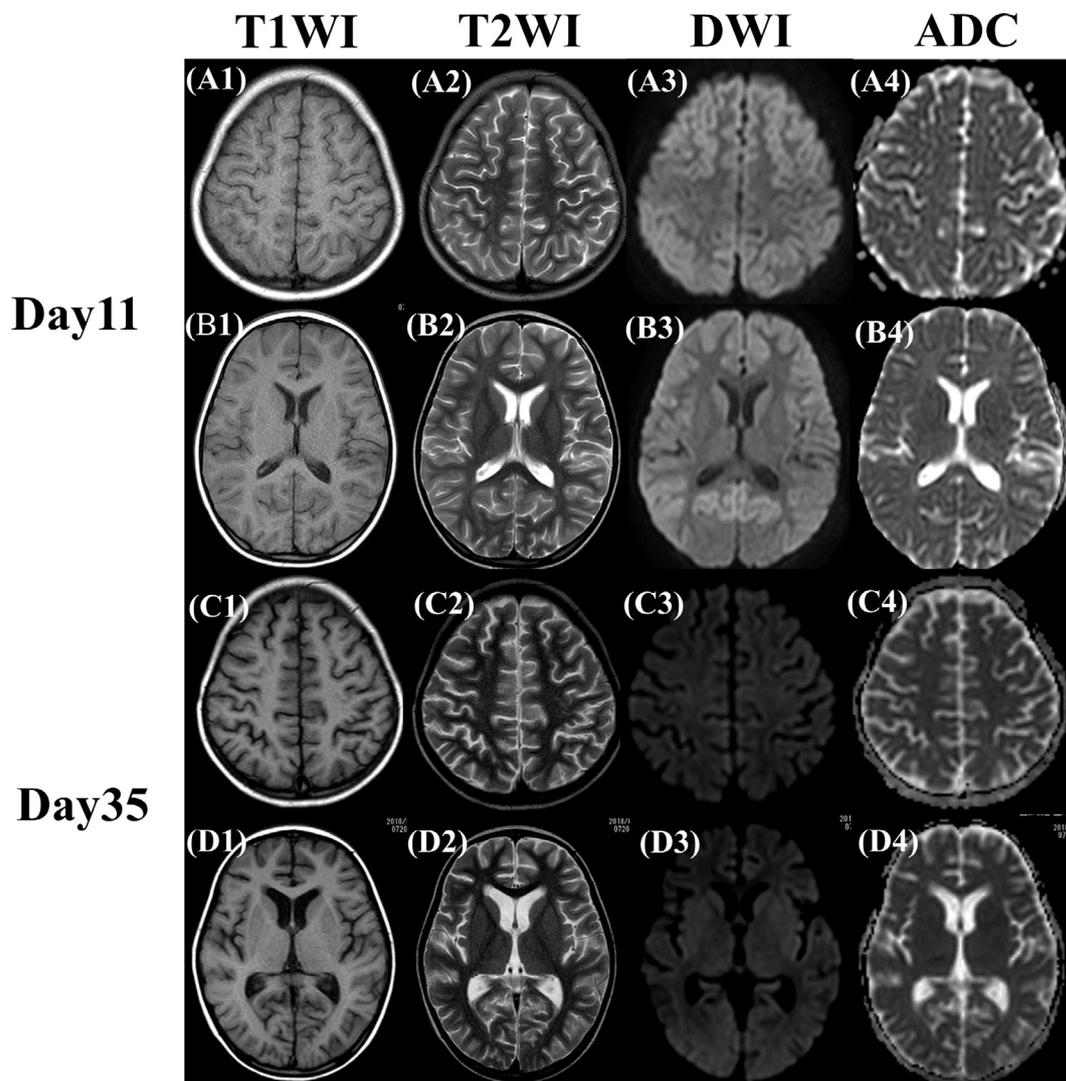


Fig. 2. Serial cranial MRI findings 11 days (A1–B4) and 35 days (C1–D4) after onset. From left to right: T1-weighted images (T1WI), T2-weighted images (T2WI), diffusion-weighted images (DWI), and apparent diffusion coefficient (ADC) map at the parietal level (A1–A4 and C1–C4) and basal ganglia-thalamus level (B1–B4 and D1–D4). DWIs on day 11 revealed lesions with reduced diffusion throughout the cortex, except in the occipital lobe, as well as perirolandic sparing (A3 and B3). Diffuse brain atrophy was observed on day 35 (C1–D4).

days after admission, she was extubated. Ten days after admission (11 days after onset), head MRI revealed lesions with reduced diffusion throughout the cortex, except in the occipital lobe, as well as perirolandic sparing (Fig. 2). Based on her clinical course, the patient was ultimately diagnosed with AESD accompanied by TTC. Acyclovir was discontinued on the same day. Seventeen days after admission, she was transferred to the previous hospital for rehabilitation. At this point, she was alert, could walk smoothly, and could eat using a spoon or fork without assistance. However, she exhibited cognitive dysfunction and could speak in single words only. Follow-up MRI 35 days after admission revealed whole-brain atrophy (Fig. 2). Although she exhibited no motor impairments and could speak in single words, she developed severe cognitive dysfunction and communication difficulties.

### 3. Discussion

In the present report, we discussed a rare case of TTC followed by symptoms of AESD in a 4-year-old patient. To the best of our knowledge, the present case is the first to document a case of AESD accompanied by TTC.

Recent studies have increasingly reported an association between seizures and TTC [4–6]. In a review of 59 reports, Finsterer et al. identified 74 adult patients (age range: 18–82 years) with seizure-triggered TTC, most of whom were female (86%). Triggering events included generalized tonic-clonic seizures, generalized status epilepticus, and complex partial seizures in 60%, 32%, and 6.4% of cases, respectively. Outcomes were relatively good, and full recovery was reported in 97% of cases [5].

Although the underlying cause of TTC in the present case remains unclear, there are several possible explanations. First, previous studies have suggested that catecholamine excess represents the main mechanism underlying the development of TTC [13]. Upon initial assessment, our patient exhibited hemoptysis as well as severe acidosis. Therefore, the intense physical stress caused by febrile status epilepticus itself may have triggered a catecholaminergic storm, which may have in turn resulted in TTC. Catecholamine support was less likely to have induced TTC because the patient's cardiac condition deteriorated prior to the initiation of catecholamine support at the previous hospital.

Second, recent studies have indicated that focal epileptic activity in the temporal lobe may cause cardiac dysfunction [7]. The temporal lobe has been associated with the regulation of autonomic function, while the insular cortex adjacent to the temporal cortex plays an important role in autonomic control of cardiac activity [6]. In our case, head MRI revealed lesions with reduced diffusion in the cortex of the temporal lobe. Thus,

prolonged seizures may have damaged this region, thereby inducing cardiac dysfunction.

Previous reports have also documented cases of transient dysautonomia or paroxysmal sympathetic hyperactivity (PSH) in patients with encephalitis or encephalopathy [8,9]. PSH is a severe dysautonomic condition that has been associated with acquired brain injuries, resulting in over-activation of the sympathetic nervous system [9]. The “disconnection” theory argues that dysautonomia of excitatory centers is due to abnormalities in higher-order control centers, while the “excitatory/inhibitory ratio (EIR) model” suggests that damage to regulatory centers in the brainstem or diencephalon releases excitatory neurotransmitters that influence spinal cord processes [10]. In the present case, we observed broad lesions throughout the cerebral cortex but not within the brainstem or lower brain levels, potentially supporting the former hypothesis. However, no previous studies have reported an association between TTC and transient dysautonomia or PSH. Therefore, further studies are required to elucidate the relationship between TTC and PSH.

Although several reports have discussed cases of AESD, none have described cases of AESD accompanied by TTC. Accumulating evidence suggests that TTC is frequently associated with neurological abnormalities such as seizure, stroke, or subarachnoid hemorrhage, which may result in underdiagnosis of TTC [11]. Because it is often reversible, patients who develop TTC under such conditions may not receive an appropriate diagnosis. Additional studies have highlighted the association between sudden unexpected death in epilepsy (SUDEP) and TTC. While SUDEP is commonly associated with a history of generalized tonic-clonic seizures [12], little is known regarding its underlying pathophysiology. Thus, it is possible that a similar condition occurs in patients who die due to AESD and TTC can be missed. Finally, acute encephalopathy is not well recognized in Europe and the United States, and most reported AESD cases have originated from Japan, potentially leading to under-reporting of acute encephalopathy accompanied by AESD.

There are currently no specific or evidence-based treatments for AESD. As such, we did not administer pulsed steroid or intravenous immunoglobulin therapy because the effects of these treatments among patients with AESD remain controversial. Targeted temperature management and/or barbiturate coma therapy may prevent biphasic seizures and neurologic sequelae. However, we were unable to administer such treatment due to the patient's hemodynamic instability.

In conclusion, we described a very rare case of TTC accompanied by features of AESD. Despite our findings, further studies are required to determine the precise relationship between TTC and acute encephalopathy.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.braindev.2018.10.002>.

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