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When the brain hurts the lung: neurogenic pulmonary edema following a first epileptic seizure

To the Editor,

We read with great interest the well-presented article entitled "When the brain hurts the heart: status epilepticus inducing tako-tsubo cardiomyopathy" published in Epileptic Disorders by Giovannini *et al.*, reviewing the unrecognized but existent entity of tako-tsubo cardiomyopathy, as a consequence of status epilepticus (Giovannini *et al.*, 2019). A high clinical index of suspicion is the key to early diagnosis of the apical ballooning syndrome in patients who experience extremely negative or positive emotions (Kotsiou and Gourgoulianis, 2017) and present with symptoms suggestive of acute coronary syndrome, particularly among those with underlying chronic illnesses (Kotsiou *et al.*, 2017), such as central nervous system (CNS) disorders.

However, the CNS could also hurt the lungs (Kotsiou *et al.*, 2017; Kotsiou and Gourgoulianis, 2017). Excess catecholamine release after sympathetic nervous stimulation underlying tako-tsubo cardiomyopathy has also been implicated in the pathophysiology of neurogenic pulmonary edema (NPE) (Kitagawa *et al.*, 2019). NPE is defined as a type of acute pulmonary edema that occurs in association with a significant illness of the CNS in the absence of primary pulmonary or cardiovascular injury (Mahdavi *et al.*, 2019). NPE following seizures has been reported in the literature as a rare, but potentially life-threatening complication of epileptic seizures (Sacher and Yoo, 2018), constituting one of the possible explanations of sudden unexpected death in epilepsy (SUDEP) in the absence of documented status epilepticus or an identifiable anatomical or toxicological cause for death at autopsy (Pezzella *et al.*, 2009; Romero Osorio *et al.*, 2017; Mahdavi *et al.*, 2019). Signs of NPE were detected in two thirds of the cases of SUDEP (Zhuo *et al.*, 2012). Data on the frequency of NPE following seizures and its clinical relevance are scarce although signs of NPE appear to be rather frequent in patients with generalized convulsive seizures (GCS) (Mahdavi *et al.*, 2019). Some observations confirm that NPE and SUDEP are mainly, but not exclusively, an issue for patients with chronic uncontrolled epilepsy (Sacher and Yoo, 2018). However, they occur also in individuals with well-controlled epilepsy or those experiencing a first epileptic seizure (Pezzella *et al.*, 2009).

Here, we present a case of an 18-year-old man without any medical disease and no history of head injury, epilepsy or drug abuse, who presented with acute respiratory failure 10 hours after experiencing an episode of GCS. On admission, he was dyspneic, hypoxic, and afebrile with a Glasgow Scale of 15/15. Arterial blood gas study performed in 0.5 fraction of inspired oxygen showed respiratory insufficiency with pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), HCO_3 and oxygen saturation (SaO_2) values of 7.46, 53 mmHg, 35 mmHg, 25.8 mmol/L, and 85%, respectively. Chest radiograph and chest computed tomography showed diffuse bilateral infiltrates (*figure 1A, B*). He had normal values for inflammatory markers and serum electrolytes. N-terminal pro-brain natriuretic peptide (NT-proBNP) was 1,450 pg/mL. Frothy pink sputum was also seen. The baseline electrocardiography (ECG) showed sinus rhythm of about 90/min and slight non-specific ST abnormalities. The echocardiography showed an elevated inferior vena cava pressure with a normal ejection fraction, normal diastolic function, no significant valvular disease, and no evidence of pulmonary hypertension. Brain magnetic resonance imaging showed no acute intracranial abnormalities, and continuous EEG, while awake, showed epileptiform activity with multiple spike-and-wave discharges and diffuse sharp-and-slow-wave complexes with a number of dominant peaks originating in the frontal lobes. No metabolic, genetic, structural CNS abnormalities or CNS infection were found. The patient was diagnosed with juvenile myoclonic epilepsy potentially facilitated by sleep deprivation, and stress that deteriorated during the preceding examination period. He was medicated with levetiracetam while he started on antibiotics for possible aspiration pneumonia, and furosemide to hastened preload reduction. The patient had a rapid clinical improvement within 48 hours with a complete recession of parenchymal infiltrates on chest radiograph (figure 1C). Faced with transient respiratory symptoms and radiographic abnormalities that resolve within 24 to 48 hours after the seizure, NPE should be strongly suspected. The proposed criteria for diagnosing NPE include:

– pulmonary edema;
– bilateral pulmonary infiltrates with a rapid resolution on chest imaging;

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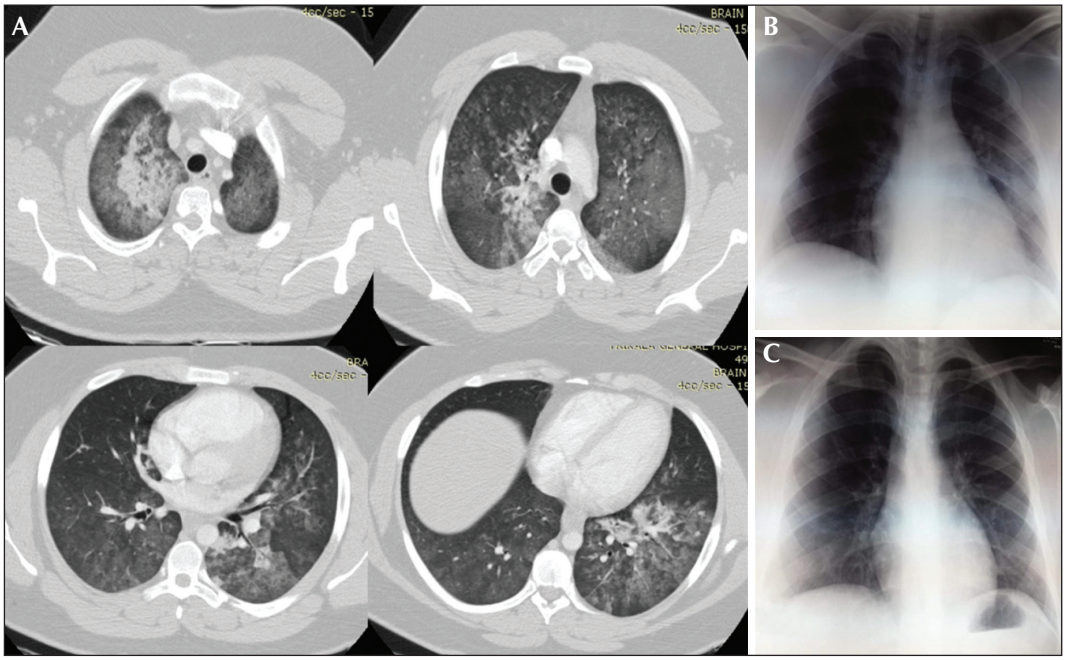

Figure 1. Chest imaging of the patient on admission (A, B) and 48 hours later (C).

– pink, frothy sputum or occasionally hemoptysis;
– partial pressure of oxygen in arterial blood (PaO_2) to fraction of inspired oxygen (FiO_2) ratio less than 200 mmHg;
– acute CNS compromise, severe enough to increase the intracranial pressure;
– absence of left atrial hypertension on echocardiography;
– and absence of other common causes of respiratory distress or acute respiratory distress syndrome (Finsterer, 2019).

We conclude that acute NPE was the most likely diagnosis in this patient after aspiration pneumonia and heart failure were excluded, and diagnostic criteria for NPE were fulfilled.

NPE is defined as acute pulmonary edema occurring shortly after a central neurologic illness, probably due to increased vascular permeability in the pulmonary capillaries triggered by inflammatory processes with resulting edema (Theodore and Robin, 1976; Romero Osorio *et al*., 2017; Mahdavi *et al*., 2019) and/or an increased adrenaline release after brain damage, resulting in pulmonary vasoconstriction, and increased vascular permeability (Zhao *et al*., 2014; Mahdavi *et al*., 2019). Interestingly, the type, duration, and frequency of seizures correlated with the onset of NPE. The incidence of NPE in partial seizures seems to be rare in contrast with GCS. In this case, the generalized epileptiform EEG activity was identified for several hours. Treatment of NPE is mainly supportive, including vasoactive compounds, diuretics, fluid supplementation, supplemental oxygen, mechanical ventilation if necessary, and control of pulmonary vascular pressures (Finsterer, 2019).

Therefore, it is of great significance to keep in mind the possible severe or even fatal acute cardiologic and/or pulmonary consequences of a neurological insult in the form of tako-tsubo cardiomyopathy or NPE, respectively, which can both occur in the early course of epilepsy and do not require long-lasting alterations of autonomic function. □

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References

Finsterer J. Neurological perspectives of neurogenic pulmonary edema. *Eur Neurol* 2019; 81: 94-102.

Giovannini G, Grassi L, Vincenzi C, Mirandola L, Meletti S. When the brain hurts the heart: status epilepticus inducing tako-tsubo cardiomyopathy. *Epileptic Disord* 2019; 21(3): 235-43.

Kitagawa T, Ishikawa H, Yamamoto J, Ota S. Takotsubo cardiomyopathy and neurogenic pulmonary edema after

carotid endarterectomy. *World Neurosurg* 2019. pii: S1878-8750(19)30085-3.

Kotsiou OS, Gourgoulianis KI. Letter by Kotsiou and Gourgoulianis regarding article. "Pathophysiology of Takotsubo syndrome". *Circulation* 2017; 136: 2291-2.

Kotsiou OS, Douras A, Makris D, Mpaka N, Gourgoulianis KI. Takotsubo cardiomyopathy: a known unknown foe of asthma. *J Asthma* 2017; 54(8): 880-6.

Mahdavi Y, Surges R, Nikoubashman O, *et al*. Neurogenic pulmonary edema following seizures: a retrospective computed tomography study. *Epilepsy Behav* 2019; 94: 112-7.

Pezzella M, Striano P, Ciampa C, Errichiello L, Penza P, Striano S. Severe pulmonary congestion in a near miss at the first seizure: further evidence for respiratory dysfunction in sudden unexpected death in epilepsy. *Epilepsy Behav* 2009; 14: 701-2.

Romero Osorio OM, Abaunza Camacho JF, Sandoval Briceño D, Lasalvia P, Narino Gonzalez D. Postictal neurogenic pulmonary edema: case report and brief literature review. *Epilepsy Behav Case Rep* 2017; 9: 49-50.

Sacher DC, Yoo EJ. Recurrent acute neurogenic pulmonary edema after uncontrolled seizures. *Case Rep Pulmonol* 2018; 2018: 3483282.

Theodore J, Robin ED. Speculations on neurogenic pulmonary edema (NPE). *Am Rev Respir Dis* 1976; 113(4): 405-11.

Zhao H, Lin G, Shi M, *et al*. The mechanism of neurogenic pulmonary edema in epilepsy. *J Physiol Sci* 2014; 64(1): 65-72.

Zhuo L, Zhang Y, Zielke HR, *et al*. Sudden unexpected death in epilepsy: evaluation of forensic autopsy cases. *Forensic Sci Int* 2012; 223(1-3): 171-5.