

Diverse Pathophysiology of Sudden Unexpected Death in Epilepsy in Children

We read with interest the review article by Garg and Sharma [1] on sudden unexplained death in epilepsy (SUDEP) in the pediatric population. We have the following comments.

A pathophysiological mechanism of SUDEP not considered by the authors is Takotsubo syndrome, also known as stunned myocardium or broken heart syndrome. Takotsubo syndrome is an acute onset, usually reversible cardiomyopathy, mainly of the left ventricle, morphologically and functionally characterized by focal or global dyskinesia, hypokinesia, or akinesia of the left ventricular myocardium, resulting in low output failure [2]. Though the outcome is usually fair, it can be fatal in isolated cases, particularly in those with the global type. The syndrome is triggered by physical or emotional stress, associated with a massive dumping of catecholamines (catecholamine storm). It is considered that the sudden overstimulation of adrenergic receptors on the surface of cardiomyocytes results in contractile dysfunction and thus acute heart failure [2]. Epilepsy is the most frequent central nervous system trigger of Takotsubo syndrome [2]. Since it can be complicated by ventricular arrhythmias [2], patients experiencing Takotsubo syndrome may not only die suddenly from acute heart failure but also from asystole or ventricular fibrillation [2].

A second pathophysiological mechanism not considered is neurogenic pulmonary edema (NPE) [3]. NPE is characterized by acutely developing pulmonary edema within minutes or hours following an acute lesion of the central nervous system [3], which usually resolves spontaneously within 24-48 hours after onset [4]. Central nervous system triggers of NPE so far reported include enterovirus 71-associated brainstem encephalitis, subarachnoid bleeding, intracerebral bleeding, traumatic brain injury, stroke, hypoxia, hydrocephalus, or epilepsy, usually with generalized tonic-clonic seizures [3]. NPE may occur after a single seizure or multiple seizures. In a retrospective study of 47 patients, NPE was found on computed tomography scans of the lungs in 19% of the patients experiencing a generalized tonic clonic seizure [5].

Overall, patients with epilepsy, particularly those with poor seizure control, polytherapy with anti-seizure drugs, poor compliance, and multiple comorbidities, should be prospectively screened for cardiac and pulmonary disease by electrocardiographic monitoring, echocardiography, stress tests, and pulmonary function tests. Epilepsy patients at risk of cardiac or pulmonary disease should receive primary prophylactic treatment to lower the risk of SUDEP.

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AUTHORS' REPLY

We thank the reader for their interest in our article [1], and for addressing additional putative pathophysiological mechanisms that may contribute to Sudden unexpected death in epilepsy (SUDEP). The authors suggest a potential role of Takotsubo syndrome. Although it has been well recognised that seizures may trigger this syndrome in adults, the role of this entity in SUDEP in general continues to be debated and in pediatric SUDEP, is definitely uncertain. In a review including 74 patients who developed Takotsubo syndrome in association with a seizure, the age range was 18-82 years [2]. Of these, a fatal outcome occurred in only two (3%) patients. This is similar to mortality reported in the International Takotsubo registry [3]. Considering the rarity of fatality, in association with the aforementioned age range, Takotsubo syndrome seems an unlikely contributor to SUDEP pathogenesis in children. Autopsy studies in SUDEP patients indicate that cardiac pathology comprises interstitial fibrosis, myocyte hyper-trophy as well as vascular wall thickening [4]. However, whether these are the effects of multifactorial influences such as anti-seizure medications or even epilepsy itself, or the cause of SUDEP remains unclear. Moreover, none of these features are pathognomonic of “active catecholamine myocarditis” pathology observed in TTS [5].

The authors also suggest a role of neurogenic pulmonary edema (NPE) in the pathogenesis of SUDEP. NPE has been consistently noted in patients with epilepsy and serves almost as a pathological biomarker for SUDEP. However, the reported degree of pulmonary edema has only been to a mild extent, as observed on autopsies in the MORTEMUS study [6]. Additionally, NPE following a seizure tends to be short-lived. Hence, both ante-mortem and post-mortem evidence suggest that NPE following seizures is a common but mild finding, making the link between SUDEP and NPE as a causative factor tenuous.

We agree with the authors' suggestion that underlying cardiac and pulmonary diseases in persons with epilepsy, particularly among those who are refractory to medical