Clinical commentary

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When the first seizure can be the last: ventricular fibrillation following a new-onset seizure

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ABSTRACT – Sudden unexpected death in epilepsy (SUDEP) is the leading cause of epilepsy-related mortality. Its mechanisms remain incompletely understood. Post-ictal arrhythmias rather than ictal arrhythmias appear to be associated with an increased risk of SUDEP. Only a handful of individuals with epilepsy who have survived ventricular arrhythmias post seizure (near-SUDEP) are reported in the literature. We report a case of ventricular fibrillation following a first-ever unprovoked seizure in a patient without epilepsy, in whom a sinus rhythm was restored following cardioversion. A defibrillator was subsequently implanted. Our case suggests that even first seizures might account for some of the many cases of unexplained ventricular fibrillation or sudden cardiac death.

Key words: epilepsy, arrhythmia, SUDEP, near SUDEP

Sudden unexpected death in epilepsy (SUDEP) is a serious complication of seizure disorders. It is the leading cause of death in drug-resistant epilepsy, and the second leading neurological cause of total years of potential life lost after stroke (Devinsky *et al*., 2016). The exact mechanism is not clearly understood, although cardiac and respiratory dysfunction are thought to account for most cases (Ryvlin *et al*., 2013). Evidence of seizure-related malignant cardiac arrhythmias is scarce, with most cases described in patients with longstanding epilepsy undergoing inpatient video-EEG monitoring (Jeppesen *et al*., 2014). Arrhythmias can occur during and after a seizure, with the latter being of particular concern due to their potential implication in sudden unexpected death in epilepsy (SUDEP) (van der Lende *et al*., 2016). Although primary ventricular arrhythmias can result in convulsive syncope (due to cerebral hypoperfusion) which can mimic epileptic seizures, ventricular fibrillation (VF) after an epileptic seizure has been reported only on a handful of occasions, all in patients with epilepsy (Espinosa *et al*., 2009; Ferlisi *et al*., 2013; Jeppesen *et al*., 2014; Seo and Sung, 2019). Here, we report a case of VF

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following a first unprovoked seizure, which was rescued by cardioversion. Our case suggests that first-ever seizures can trigger malignant arrhythmias, and may account for some of the many cases of unexplained VF or sudden cardiac death.

Case study

The patient in context is a 24-year-old critical care nurse with no significant past medical history. In particular, she had no personal history of syncope or prior unrecognised epileptic seizures, head trauma, meningoencephalitis or febrile seizures, nor a family history of epilepsy or sudden cardiac death. She was on no regular medications, was a non-smoker, had rare alcohol consumption and denied intravenous drug use. There were no identifiable seizure precipitants. A colleague saw her fall back on her chair to the ground and have a generalized tonic-clonic seizure, characterised by loss of consciousness, upward eye rolling, diffuse tonic stiffening, and later clonic limb movements, lasting overall ~90 seconds. The seizure was associated with urinary incontinence. She subsequently denied any warning to the seizure. The emergency team and resuscitation equipment arrived while she was still convulsing. Post-ictally, she was noted to be cyanotic with agonal breathing. There was an absent pulse and cardiopulmonary resuscitation (CPR) was commenced. Defibrillator pads were placed and a check for initial rhythm by multiple emergency physicians confirmed VF. A single 200-Joule DC cardioversion was delivered restoring her rhythm to sinus tachycardia with output. Over the following 15 minutes, she had two additional generalised tonic-clonic seizures requiring sedation and intubation. Rhythm on the telemetry during these next two seizures showed sinus tachycardia only, with no further ventricular arrhythmias. Initial laboratory tests showed lactate at 2.5 mmol/L and normal full blood counts, electrolytes, renal function, liver function and thyroid function. Urine drug screening showed only benzodiazepines (resulting from midazolam administration for sedation). Serial high-sensitivity troponin I was within normal limits. ECG revealed sinus tachycardia with a QTC of 420 ms based on Bazett's formula. Brain CT and MRI, and an EEG (performed on Day 2 post-seizure) were normal. Echocardiography showed normal biventricular function, CT coronary angiography showed a calcium score of 0 with normal coronary arteries, and a cardiac MRI showed a structurally normal heart with no scar. She was commenced with levetiracetam at 2,000 mg/day, and extubated within 24 hours. Inpatient telemetry (ECG) monitoring for more than five days showed sinus rhythm throughout and no transitory ECG alterations. She made a good neurological recovery with no further seizures, and was discharged with a subcutaneous implanted cardioverter defibrillator. A subsequent sleep-deprived EEG was normal during wakefulness, drowsiness and Stage II sleep. At her last follow-up appointment four months post-seizure, she was still seizure-free on reduced levetiracetam doses (1,000 mg/day).

Discussion

SUDEP has been defined as the "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause of death" (Nashef, 1997). Near-SUDEP occurs when a patient with epilepsy survives resuscitation for more than one hour after a cardiorespiratory arrest that has no structural cause identified after investigation (Nashef, 1997). Although the exact pathophysiological mechanisms of SUDEP remain incompletely understood, most cases appear to be associated with profound cardiorespiratory dysfunction (Ryvlin *et al.*, 2013). Cardiac dysfunction includes seizure-related arrhythmias, with post-ictal arrhythmias likely being more sinister than ictal arrhythmias (*table 1*). The cause of these arrhythmias is unclear, but may be related to the profound autonomic nervous activation (with a shift towards sympathetic overactivity) during a seizure, QTC shortening or prolongation, toxic effects of antiseizure medications, or inherited channelopathies which can co-exist in the heart and brain such as *KCNQ1* mutations causing Long QT syndrome (González *et al.*, 2018; Seo and Sung, 2019). In the present case, VF was possibly triggered by tonic-clonic seizure-related alterations of cardiac repolarisation (QT intervals, T wave alternans), thereby facilitating the onset of VF (Surges *et al.*, 2010). Respiratory dysfunction includes centrally mediated apnoea, suffocation and laryngeal spasm. Risk factors associated with SUDEP include the presence and frequency of generalized tonic-clonic seizures, not being seizure-free for one to five years, and a lack of nocturnal supervision (Harden *et al.*, 2017).

Only four cases of post-ictal VF have been published in English (Espinosa *et al.*, 2009; Ferlisi *et al.*, 2013; Jeppesen *et al.*, 2014; Seo and Sung, 2019). All patients had an established diagnosis of epilepsy, of whom three had longstanding drug-resistant epilepsy and were taking multiple antiseizure medications (Espinosa *et al.*, 2009; Ferlisi *et al.*, 2013; Jeppesen *et al.*, 2014). In all cases, VF was preceded by a tonic-

Table 1. Characteristics of ictal vs post-ictal arrhythmias (largely based on data from van der Lende *et al*. [2016]).

	Ictal arrhythmias	**Post-ictal arrhythmias**
Severity	Typically self-limiting	Life-threatening
Termination	Spontaneous	Can lead to death
Origin	Most reported cases associated with temporal lobe seizures	Reported in focal-onset as well as in generalised-onset seizures
Type of seizure	Focal seizures	Typically after tonic-clonic seizures[a]
Type of arrhythmia (excluding sinus tachycardia)	Bradycardia/asystole, atrioventricular block[b], atrial flutter	Asystole[c], atrioventricular block[b], atrial fibrillation[d], VF

[a]Focal-to-bilateral tonic-clonic seizures, generalised tonic-clonic seizures, or unknown-onset tonic-clonic seizures; [b]In the study of van der Lende et al. (2016), (11)/13 cases of atrioventricular block identified in the literature were ictal, and the remaining two were post-ictal; [c]Occurring predominantly secondary to severe hypoxemia; [d]In the study of van der Lende et al. (2016), most cases of atrial fibrillation identified in the literature (12/13) were post-ictal, however, one case of atrial fibrillation during a focal impaired awareness seizure was also identified. VF: ventricular fibrillation.

clonic seizure and CPR was performed. In three cases, sinus rhythm was restored and the cases were classified as near-SUDEP (Espinosa *et al*., 2009; Ferlisi *et al*., 2013; Seo and Sung, 2019). The fourth patient instead died despite CPR, and was therefore classified as SUDEP (Jeppesen *et al*., 2014). Our case extends the spectrum of post-ictal VF, in that VF occurred after a first-ever (tonic-clonic) seizure in a patient who did not meet the criteria for epilepsy (*i.e.* three seizures <24 hours apart and a probability of recurrence of <60%). Thus, this case does not qualify as a near-SUDEP.

Our case highlights the potential risk of mortality associated with a first unprovoked seizure. In epidemiological studies, the standardised mortality ratio (SMR) in individuals with a newly diagnosed unprovoked seizure has been found to range from 2.3 to 4.1, with estimates varying according to the study population and design (Hauser and Beghi, 2008). The risk appears to be greatest in the first two years after diagnosis, in younger individuals, and when the aetiology of the seizure is known (Hauser and Beghi, 2008).

Remarkably, in up to 60% of cases with VF or sudden cardiac death, no underlying cause can be identified despite extensive clinical investigations and genetic workup (Al-Khatib *et al*., 2018). Our case suggests that first-ever seizures, particularly if unwitnessed, might account for at least some of these cases. □

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) When are arrythmias secondary to seizures most dangerous?

A. During a seizure
B. During the post-ictal period
C. They are never dangerous
D. They are always dangerous

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".