

Sudden unexpected death in epilepsy patients is often misdiagnosed as sudden cardiac death

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Neurology® 2017;89:878–879

Sudden unexpected death in epilepsy patients (SUDEP) represents the second main neurologic cause of years of potential life lost, following stroke, with a cumulative lifetime risk reaching 8% for childhood-onset epilepsy.¹ In light of these worrying figures, the American Academy of Neurology (AAN) has recently published practice guidelines on the risk of SUDEP. These guidelines emphasize the “considerable uncertainty” of SUDEP incidence in adults with epilepsy, currently estimated at 1.2/1,000 patient-years (95% CI 0.64–2.32).² Difficulties in assessing the epidemiology of SUDEP are several, including large variation in SUDEP risk across epilepsy populations (up to 100-fold difference between newly diagnosed and refractory epilepsy)³ and a lack of a SUDEP code in the current *International Classification of Diseases* (ICD). As a result, SUDEP is underreported and underrecognized by medical examiners, coroners, and clinicians who complete death certificates.⁴ In fact, many physicians view SUDEP as a sudden cardiac death (SCD), for which the relation to seizures is often uncertain. This view is at odds with evidence gathered during the last decade, suggesting that most SUDEP occurs in the immediate aftermath of a generalized tonic-clonic seizure through centrally mediated autonomic failure, distinct from mechanisms at stake in SCD.⁵ Progress in distinguishing SUDEP from the general framework of SCD is thus needed.

In this issue of *Neurology*®, Devinsky et al.⁶ address this by reassessing a unique population-based cohort of 525 autopsy-assessed adult SCD cases collected in the San Francisco Postmortem Systematic Investigation of Sudden Cardiac Death Study (POST SCD). Two epileptologists, experts in SUDEP, reviewed all cases with a history of seizures or epilepsy and compared their conclusions regarding the cause of death (COD) to the original adjudication provided by the POST SCD multidisciplinary team, composed of pathologists, electrophysiologists, and vascular neurologists.⁶ While the latter reported 15 epilepsy cases, including 6 SUDEP (all definite), epileptologists identified 25 epilepsy cases, including 18

SUDEP (6 definite, 2 definite-plus, and 10 possible), as well as 5 alcohol-related acute symptomatic seizures that could have contributed to death.⁶ Overall, SUDEP accounted for 3.4% of all autopsy SCDs⁶ and 8.3% in the range of 18–40 years (O. Devinsky, personal communication, May 9, 2017).

The two-thirds lower rate of SUDEP adjudication by the POST SCD multidisciplinary team reflected underdiagnosed epilepsy, based on patient’s medical history, and differences in the interpretation of autopsy and forensic findings. In 2 patients aged 29 and 52 years with subendocardial fibrosis, including one with moderate thickening of his mitral valve, the POST SCD multidisciplinary team determined COD as cardiac hypertensive heart disease and cardiomyopathy, whereas epileptologists adjudicated a definite SUDEP plus based on typical circumstances of death, lack of lethal cardiac condition, and knowledge that subendocardial fibrosis is commonly observed in SUDEP patients.^{4,6} Similarly, the POST SCD multidisciplinary team adjudicated chemical overdose as COD in 2 patients with chronic drug abuse, while epileptologists considered their relatively low drug levels less likely to have resulted in death than a SUDEP, leading to a diagnosis of possible SUDEP.⁶

While the POST SCD study offers the strengths of a robust community-based assessment of SCDs, with autopsy available in 97% of cases, it might still underestimate the true prevalence of SUDEP, since a history of seizure or epilepsy might have been missed in a yet unknown proportion of patients.⁶ Few data are available for comparison. A nationwide Irish study of 292 suspected SCDs in patients aged 14 to 35 years reported 22 SUDEP (7.3%) and 116 autopsy-confirmed SCDs (39.7%, excluding SUDEP).⁷ However, criteria for adjudicating SUDEP were not available.⁷ Most other SCD studies fail to mention SUDEP or epilepsy or would merely consider seizure as the consequence of lethal cardiac arrhythmia.⁸ One notable exception is a recent study of SCDs in patients aged 35 years or younger, in which those with a history of epilepsy were excluded.⁹ Yet, several findings suggested that an occult seizure disorder might

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

be at play in some of the 40% of patients with unexplained SCDs.⁹ First, 6% of these patients showed probable pathogenic variants in epilepsy genes.⁹ Second, death occurred at night and during sleep in 67% and 48% of these patients, respectively, and more frequently than in SCDs associated with a cardiac pathology.⁹

The POST SCD study does not provide direct estimates of the incidence of SUDEP in the general population. However, these can be extrapolated from the incidence of SCDs in North America, estimated at 98.1/100,000.¹⁰ Using the multidisciplinary team assessment,⁶ the incidence of definite and probable SUDEP would be about 1.1/100,000 vs 1.5/100,000 using the epileptologists' adjudication. Both figures are only slightly greater than that calculated from community-based SUDEP incidence studies, 0.81/100,000 (95% CI 0.68–0.97).¹

Another issue that needs to be considered when assessing SCDs and SUDEP, comparatively, is their major difference in age distribution. While SUDEP primarily affects young adults, with more than two-thirds of cases occurring before the age of 40,¹ less than 1% of SCDs are observed in individuals younger than 35 years, with an incidence of 1–3 per 100,000 patient-years in this age group.¹⁰

The findings reported in this issue of *Neurology* by Devinsky et al.⁶ stress the necessity for more collaboration among medical examiners, coroners, and neurologists to improve the recognition and coding of epilepsy-related deaths and SUDEP. This is important not only for advancing SUDEP research but also for bereaved relatives of individuals who die of SUDEP. Introducing SUDEP as a specific code within the ICD-11 classification should be a priority for all stakeholders, with the understanding that the majority of SUDEP are simply not SCDs.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

P.R. reports no disclosures related to the manuscript. G.D.C. receives a stipend in his editorial capacity for *Neurology*. Go to Neurology.org for full disclosures.

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