Received: 24 January 2019 | Revised: 13 May 2019 | Accepted: 19 May 2019

DOI: 10.1002/epi4.12342

SHORT RESEARCH ARTICLE

Epilepsia Open® Open Access

SUDEP in patients with epilepsy and nonepileptic seizures

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Funding information
Lundbeck Pharmaceuticals; American Epilepsy Society; Finding A Cure for Epilepsy and Seizures

Abstract

We report 13 SUDEP cases in the North American SUDEP Registry with both psychogenic nonepileptic seizures (PNES) and epileptic seizures (ES) among a consecutive series of 231 cases (excluding epileptic encephalopathies). On average, cases of PNES + ES died at a younger age (23 ± 11 years) than the ES-only cohort (30 ± 14 years), and died an average of 3 years after PNES diagnosis. We found no statistically significant confounding cardiac, respiratory, or psychiatric comorbidities and equal rates of anti-seizure medication adherence, although there was a trend for higher rates of psychiatric disorders in the PNES group. Our findings confirm that patients with comorbid ES and PNES can die from SUDEP and that there may be a high-risk period after the diagnosis of PNES is made in patients with comorbid ES. Such patients should be closely monitored and provided with coordinated care of both their epilepsy and psychiatric disorder(s).

KEYWORDS

differential diagnosis, epilepsy monitoring, paroxysmal events, psychogenic nonepileptic seizures

1 | INTRODUCTION

Psychogenic nonepileptic seizures (PNES) are paroxysmal behaviors that mimic seizures, but result from psychological processes, and lack the electrophysiological changes in epileptic seizures (ES). Because more than 10% of patients with PNES have concurrent or prior ES, distinguishing ES from PNES may be challenging, although seizure semiologies are usually distinct.[1] Clinical features such as event provocation by stress or suggestion, reports of ability to control seizure activity, and preservation of consciousness during convulsive motor activity may lead ES to be incorrectly diagnosed as PNES. Differentiating ES from PNES in patients with both disorders or between patients with only ES or PNES is critical. Anti-seizure medication (ASM) overuse in PNES patients without comorbid ES can cause disabling side effects and exacerbate psychiatric comorbidities.[2] Conversely, misdiagnosis of ES as PNES can lead to dangerous omission of effective ASMs.[3] PNES are frequently associated with a history of severe psychological stress, and affected patients have high rates of post-traumatic stress disorder, mood, and pain disorders.[4]

Psychogenic nonepileptic seizures are associated with increased morbidity and mortality. Patients are exposed to dual stigmas of "epilepsy" and "psychiatric disorder considered self-generated." PNES patients are often hospitalized and administered unnecessary and often harmful therapies.[5,6] The twofold increased mortality rate in PNES results from several causes, including iatrogenic mortality such as intubation for prolonged PNES and aggressive ASM therapies,[7] comorbid physical (eg, difficulty ambulating due to neurological or conversion disorders) and mental illnesses,[7] injuries sustained during PNES (eg, falls),[8] drug overdose, and suicide.[5] Notably, chronic pain disorders, opiate abuse, and suicide attempts (23% in PNES) are significantly more common in patients with only PNES versus only ES.[4,9]

TABLE 1 Clinical features of SUDEP patients with and without PNES

	PNES + ES (n = 13)	ES only (n = 231)
Age at death (mean [SD])	23 (10.8)	30 (14.0)
Age of epilepsy onset (mean [SD])	11 (7.4)	14 (11.7)
Age of PNES diagnosis (Mean [SD])	20 (11.3)	–
Type of epilepsy		
Focal	7	100
Generalized	2	42
Both	0	8
Unclassified	4	89
Side of epileptic focus (focal only)		
Right	2	29
Left	0	19
Bilateral	2	15
Lifetime GTCS frequency		
0-10	2	66
11-100	6	51
101-500	2	20
500+	1	14
Nocturnal GTCS?		
Yes	6	55
No	0	10
Nocturnal supervision?		
Yes	2	9
No	11	170

Note: Missing values are unreportable due to insufficient medical records or interview recall.
Abbreviations: ES, epileptic seizures; GTCS, generalized tonic-clonic seizure; PNES, psychogenic nonepileptic seizures; SUDEP, sudden unexpected death in epilepsy. Nocturnal supervision is defined as parental use of a baby monitor, video surveillance, or other method to identify seizures.

Patients with coexisting ES and PNES, however, may be most vulnerable to premature mortality because they also bear the risks of poorly controlled ES. Here, we report 13 cases of ES and PNES in patients who died from sudden unexpected death in epilepsy (SUDEP).

2 | METHODS

Since October 2011, the North American SUDEP Registry (NASR) has enrolled decedents with epilepsy, living epileptic controls, first-degree relatives of SUDEP cases, and control decedents with/without epilepsy. We reviewed all cases through December 2018. Next-of-kin (NOK) decedents were referred to NASR from physicians, medical examiners, or coroners, and advocacy groups (eg, NIH Center for SUDEP Research, Epilepsy Foundation/SUDEP Institute, Dravet Syndrome Foundation, Dup15q Alliance, Danny Did Foundation), or self-referred through online search, recorded at the time of enrollment. All next of kin provided written informed consent, and this study was approved by the NYULMC Institutional Review Board.

All NASR cases with sufficient information were reviewed and independently adjudicated for SUDEP classification by two epileptologists using the Nashef et al criteria.[10] In the event of disagreement, a third epileptologist reviewed cases to reach consensus. In this review, we included only cases of definite, definite plus, and probable SUDEP, excluding decedents with epileptic encephalopathies (eg, Dravet, Doose, West, and Lennox-Gastaut syndromes).

2.1 | Data collection

A research assistant conducted a structured telephone interview, including questions about social/familial history, medication history/adherence, seizure history/semiology, health state prior to death, and circumstances of death (for detailed methodology, see Ref.[11]). Medical records and diagnostic tests (consisting of reports and original data for EEGs and video-EEGs, brain MRIs, and ECGs) were obtained from providers where the decedent had received care. Seizure types, epilepsy etiology, MRI findings, and EEG results were abstracted using the NIH Common Data Elements for epilepsy.[12] Using the available data, we adjudicated seizure types, epilepsy syndrome, EEG findings, ECG tracings, and MRI findings by a NASR neurologist or cardiologist to confirm diagnostic validity. Central tendencies were expressed as mean ± SD.

Psychogenic nonepileptic seizures diagnosis was primarily based on medical records reviewed by a NASR epileptologist. In 12 cases, a diagnosis of PNES was found in medical records from a treating physician. Nine of these had PNES confirmed by (v)EEG, by symptoms inconsistent with epileptic seizure and lack of EEG correlates. One case had seizures diagnosed by physician upon description by patient's mother, confirmed by epileptologist post-mortem (OD). These events were provoked by disruptions of daily activity or difficulties in school. For example, seizures would immediately precede braces being tightened. One additional case had PNES listed in the autopsy report, without medical records available to corroborate this diagnosis. In this case, a NASR epileptologist confirmed PNES as a very probable additional diagnosis to epilepsy, based on seizure descriptions from the next-of-kin interview, which detailed extensive childhood trauma, other stress-related psychological sequelae, and partially aware convulsive activity for >30 minutes. We obtained a copy of (v)EEG used to diagnose PNES in nine of nine cases.

2.2 | Statistical methods

Chi-square tests were used to compare ES + PNES and ES-only SUDEPs for commonly reported comorbidities and categorical ASM adherence. Mann-Whitney *U* tests were used to compare ages at time of death and at epilepsy onset for both ES + PNES and ES-only groups. (version 23; IBM).

3 | RESULTS

Among 231 definite and probable SUDEP cases, we identified 13 (6%) with comorbid PNES. These cases included seven definite, one definite plus, and five probable SUDEP. PNES/ES SUDEP cases were younger at the time of death (22.7 ± 10.8 years) than the ES-only SUDEP cases (30.4 ± 14.0 years; $P = 0.043$). Among PNES/ES patients, the mean age of epilepsy onset was 11.2 ± 7.4 years vs 14.0 ± 11.7 years in the overall cohort, with no significant difference between groups ($P > 0.05$). The mean age of PNES diagnosis was 20 ± 11.3 years. 54% of PNES cases were male versus 64% in the ES-only cohort.

Among the 13 PNES cases, the most common comorbidities were depression (54% in the PNES/ES vs 34% in the ES-only cohort), ADHD/ADD (31% vs 18% in ES-only cohort), and sleep disorder (31% vs 16% in ES-only cohort), and there was no difference ($P > 0.05$) between ES and PNES/ES groups. Prevalence of cardiac, respiratory, and psychiatric comorbidities did not differ between ES and PNES/ES groups ($P > 0.05$). Clinical characteristics of both PNES/ES and ES-only cohorts are summarized in Table 1; detailed accounts of PNES and ES for each case are described in the Table S1.

Eight PNES/ES SUDEP cases had a family history of ES. Two PNES/ES decedents had siblings who also died from epilepsy: One was definite SUDEP, and one was less well defined.

All cases had one or more significant stressors identified as the potential cause of PNES, most often physical, emotional, or sexual abuse. Other factors included substance abuse in self or family, debilitating comorbid health conditions, or significant financial stressors. The case without history of abuse, drug/alcohol addiction, or work-related stress was a high school valedictorian who slept 2-3 hours per night for months preceding her death. All PNES cases with available current medication history (n = 12/13) were prescribed anti-seizure medication (ASM) at the time of death, most often lamotrigine (6), levetiracetam (3), and lacosamide (3). Rate of NOK reported ASM adherence in PNES (73%) was slightly higher than in the ES-only cohort, with only 54% of cases with sufficient medication histories (n = 177/218) taking ASMs as prescribed. This difference was not significant ($P > 0.05$). Nine PNES cases had MRI reports: six were normal, and three had pathological changes, including posterior fossa arachnoid cyst (1), left temporoparietal encephalomalacia and ventricular shunt catheter (1), and frontopolar cortical dysplasia (1).

4 | DISCUSSION

Among our 231 SUDEP cases, we identified 13 patients with ES and PNES. The epilepsy associated with PNES in our patients was fatal, emphasizing that comorbid ES/PNES can be disabling and potentially deadly due to either disorder. Compared to SUDEP cases with only ES, those with ES and PNES were younger at the time of death, had similar ages of epilepsy onset, and had similar rates of neuropsychiatric comorbidity. The average interval between diagnosis of PNES and SUDEP was only three years, suggesting that, for some individuals with epilepsy, the occurrence of significant life stressors (eg, physical, emotional, or sexual abuse, and major financial or relationship issues) may lead not only to conversion symptoms (ie, PNES) but may also to increased risk of lethal seizures or other factors that contribute to SUDEP. Since ASM nonadherence rate was similar between ES/PNES and ES-only SUDEP cases, this does not appear to be a confounding mechanism. Further, lack of clinically significant neuropsychological variance between the ES-only and PNES/ES groups indicates that related psychiatric comorbidities do not contribute to increased SUDEP risk.

Psychogenic nonepileptic seizures patients without comorbid ES have more than twofold higher rates of mortality compared to the general population,[13] emphasizing the gravity of this disorder and the failure of neurologists and psychiatrists to effectively treat these patients. PNES patients should be evaluated and promptly treated for comorbid psychiatric disorders (eg, depression and anxiety), suicidal ideation or plans, and substance (especially opiate) abuse disorders. It is essential that PNES patients are treated with respect and the validity and seriousness of their disorder recognized. Diagnosis of a psychiatric disorder in a patient/family focused on a neurological etiology, together with the perceived stigma, can lead many patients to reject the diagnosis and seek affirmation of a neurological disorder elsewhere. As we counsel epilepsy patients about their increased risks of morbidity and mortality, we should similarly counsel PNES patients and families.

The prevalence of PNES is estimated as 5%-10% of all epilepsy patients,[14] affecting as many individuals as Parkinson's disease or multiple sclerosis.[15] The frequency of PNES is 15%-30% among patients admitted to epilepsy monitoring units (EMUs), a population biased with high rates of treatment-resistant seizures, diagnostic challenges, and suspected PNES cases.[1,16] Among EMU-confirmed cases of PNES, ~10% have current or prior comorbid epilepsy.[1] Our findings suggest that among epilepsy patients

who develop PNES after a major stressor, neurologists should address these events promptly and with tact, as we find PNES diagnosis in the NASR cohort to shortly (<3 years) precede SUDEP.

There are multiple limitations to our study, including selection and recall bias, and incomplete or limited medical records. The NASR is primarily based on referrals from lay organizations (eg, Epilepsy Foundation) and epileptologists, with only a minority (33%) derived from a community population review of all seizure/epilepsy cases identified at the San Diego Medical Examiner's Office. NOK interviews, most of which were done over one month after the death of their family member, are subject to recall bias. Incomplete and scarce medical records in many cases referred by medical examiners make it possible that some ES-only SUDEP deaths may have had PNES diagnosed, but those records were not available. In other cases, patients only diagnosed with ES, even at tertiary care epilepsy centers, may have also had unrecognized PNES.

Both ES and PNES + ES groups had similar ages of epilepsy onset, age at death, and ASM adherence rates. However, in cases with comorbid PNES, SUDEP occurred an average of 3 years after PNES diagnosis. Our findings suggest that epilepsy patients who are subsequently diagnosed with PNES may be at high risk of SUDEP over the next 5 years, despite ASM adherence and lack of confounding contribution from cardiac, respiratory, or psychiatric conditions. Further studies are needed to confirm this potential "high-risk interval," but it may offer opportunities to understand novel risk factors for SUDEP and develop targeted interventions to prevent SUDEP in a very high-risk population.

ACKNOWLEDGMENTS

NASR is supported by grants from Finding A Cure for Epilepsy and Seizures, Lundbeck Pharmaceuticals, and the American Epilepsy Society.

CONFLICT OF INTEREST

Daniel Friedman serves on the executive committee of the North American SUDEP Registry and is on the advisory board of the Epilepsy Foundation of America SUDEP Institute. He has performed contracted research for Epitel, Empatica, and Neuropace. He holds ownership interest in Neuroview Technology. He receives salary support from the nonprofit Epilepsy Study Consortium. He has consulted or serves on advisory boards for Eisai and Penumbra. He has received an honorarium for educational materials from Neuropace. He also receives research support from NINDS, Epilepsy Foundation, the Centers for Disease Control and Prevention, and UCB Pharmaceuticals. Orrin Devinsky has equity interest/role on advisory board for: Receptor Life Sciences (Chief Medical Officer), Tilray, Engage, Papa and Barkley, Empatica, Q-state, and Rettco. He is Principal Investigator for the North American SUDEP Registry and services on the Executive Committee for the Epilepsy Foundation SUDEP Institute. Chloe Verducci reports no competing financial disclosures. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Verducci C, Friedman D, Devinsky O. SUDEP in patients with epilepsy and nonepileptic seizures. *Epilepsia Open*. 2019;4:482–486. https://doi.org/10.1002/epi4.12342