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Sudden Unexpected Death in Epilepsy, Peri-ictal Physiology and the SUDEP-7 Inventory

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SUMMARY

Sudden unexpected death in epilepsy (SUDEP) is a significant public health burden. Epidemiological studies have identified clinical SUDEP risk factors across large populations, but the means to apply this information to individual patients are lacking. The SUDEP-7 Inventory was developed as a marker of clinical SUDEP risk and has been used in studies of potential SUDEP biomarkers. We retrospectively reviewed clinical data from 16 patients dying of SUDEP and 48 matched living epilepsy controls to determine whether individuals succumbing to SUDEP could be distinguished from living epilepsy controls using the revised SUDEP-7 Inventory, the absolute number of clinical risk factors as identified by an ILAE meta-analysis (ILAE score), and physiological characteristics previously associated with SUDEP risk. Mean revised SUDEP-7 Inventory score was 3.3 ± 2.0 in SUDEP cases and 3.8 ± 2.3 in controls ($p=0.39$). Mean ILAE score was 2.4 ± 1.1 in SUDEP cases and 2.6 ± 1.4 in controls ($p=0.62$). There were no significant differences in inter-ictal heart rate variability (measured by RMSSD), peri-ictal cardiorespiratory dysfunction and post-ictal generalized EEG suppression (PGES) between the groups. This demonstrates that a reliable instrument for individual SUDEP risk stratification is lacking and highlights the need for improved understanding of SUDEP pathophysiology and individual risk determination.

Keywords

Epilepsy; SUDEP; SUDEP-7; Peri-ictal physiology; heart rate variability; predictors of SUDEP

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death directly related to epilepsy, accounting for 7–17% of deaths in epilepsy patients and up to 50% in those with refractory epilepsy.¹ SUDEP ranks second only to stroke in potential years of life

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DISCLOSURE OF CONFLICTS OF INTEREST

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ETHICAL PUBLICATION STATEMENT

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.

lost due to neurological disease, therefore representing a significant public health burden.² The means to individually target SUDEP risk reduction interventions, however, are currently lacking. This has profound implications for the counseling and treatment of individual patients, and the conduct of research into SUDEP pathophysiology and prevention.

Large, community-based, case-control studies have contributed to our knowledge of SUDEP risk factors, sometimes with conflicting results. A combined analysis of several such studies identified five key independent SUDEP risk factors³ but the presence of these alone does not clearly define individual risk. A clinical rating scale, the SUDEP-7 Inventory, provided weighting to individual risk factors from a single epidemiological study⁴, in an attempt at individual risk stratification.⁵ This inventory has been used as a marker of SUDEP risk in studies of potential physiological biomarkers, including heart rate variability (HRV), peri-ictal cerebral oxygenation, and post-ictal generalized EEG suppression (PGES).^{6,7,8} However, the SUDEP-7 Inventory has not been clinically validated as a predictor of individual SUDEP risk.

We sought to determine whether the revised SUDEP-7 Inventory, the presence of independent clinical SUDEP risk factors, or proposed SUDEP biomarkers could distinguish between individuals dying of SUDEP and matched living epilepsy patient controls. We hypothesized that individuals dying of SUDEP would have higher SUDEP-7 scores and a greater number of clinical risk characteristics than controls.

METHODS

We retrospectively identified 16 cases of definite or probable SUDEP and 48 living epilepsy patient controls, matched for gender, age within 10 years, and epilepsy syndrome, with clinical contact documented within the last 18 months. The study was approved by the local institutional review board.

We reviewed medical records to calculate revised SUDEP-7 Inventory scores,⁵ the elements of which are summarized in Table 1, and ILAE scores, defined as an un-weighted total of independent risk factors identified in the ILAE combined analysis.³ When available, we reviewed ictal EEG recordings to identify physiological markers previously linked to SUDEP, including 1. Peri-ictal cardiac arrhythmia, defined as an increase or decrease in heart rate $\geq 50\%$ of baseline and/or definite change in rhythm, repolarization and/or conduction,⁹ 2. Peri-ictal respiratory dysfunction, defined as reliable pulse oximeter recording of $<90\%$ saturation or agonal breathing, which was labored requiring accessory muscles and/or apnea or bradypnea/tachypnea,¹⁰ defined as a cessation of breathing or obvious decrease or increase in breathing rate as determined by observing video-EEG and/or by respiratory artifact on EEG, and 3. Post-ictal generalized EEG suppression (PGES), as defined by Lhatoo, et al¹¹. We also calculated the root mean square of differences of successive R-R intervals (RMSSD), previously associated with SUDEP-7 Inventory scores^{6, 12} as a measure of HRV. This data was derived from single lead EKGs during inter-ictal EEG recordings over 120 consecutive R-R intervals. Lastly, we examined whether a history of frequent or any generalized or focal to bilateral tonic-clonic seizures (GTCS/

FBTCS) alone could distinguish between the two groups, as this is considered the most important clinical factor in determining SUDEP risk.^{1, 3, 4}

Differences between groups were analyzed using the paired T-test and Fisher's exact test, with p-values less than 0.05 considered statistically significant.

RESULTS

Table 2 summarizes the results. Each group contained 50% men and 50% women. Mean age was 42 (range 18–63) in the SUDEP group, and 41 (range 10–73) in the control group. In the SUDEP group, 13 (81%) had focal epilepsy, four (30%) of whom had undergone epilepsy surgery. One (6%) had a generalized onset epilepsy syndrome and two (13%) had an unknown epilepsy syndrome. In the control group, 40 (83%) had focal epilepsy, six (15%) of whom had undergone epilepsy surgery. Five (10%) had a generalized onset epilepsy syndrome, and three (6%) had an unknown epilepsy syndrome. There was no significant difference in age, duration of epilepsy, or epilepsy syndrome between the groups ($p=0.72$, $p=0.48$, $p=0.13$).

The mean revised SUDEP-7 Inventory score was 3.3 ± 2.4 (range 0–7) in SUDEP cases, and 3.8 ± 2.3 (range 0–9) in controls. The mean ILAE score was 2.4 ± 1.1 (range 0–4) in SUDEP cases, and 2.6 ± 1.4 (range 0–5) in controls. These differences were not statistically significant ($p=0.39$ and 0.62 respectively). Seven SUDEP cases and 32 controls had a history of FBTCS within the last year, with three SUDEP cases and 16 controls having >3 FBTCS in the past year. These differences were not statistically significant ($p=0.47$ and 0.54 respectively).

In the SUDEP group, seven patients had video-EEG recorded seizures, six with adequate post-ictal EEG data to assess for PGES. Of these, three had FBTCS with PGES (range 11–34 seconds). Among controls, 35 patients had video-EEG recorded seizures. Nine had FBTCS, five with PGES (range 18–65 seconds). PGES was not seen with other seizure types in either group. A significant difference ($p=0.042$) existed for PGES over all seizures. However, PGES is primarily associated with FBTCS⁹, and no significant difference was seen when considering only this seizure type ($p=0.64$). Only one subject in the control group had PGES>50 seconds with one seizure.

The mean RMSSD was 23.5 ± 8.0 in SUDEP cases and 37.3 ± 22.2 ($p=0.18$) in controls. Interpretable peri-ictal EKG was available in six SUDEP cases, two with peri-ictal arrhythmia (both tachycardia), and 35 controls, ten of whom had peri-ictal arrhythmia (one with bradycardia and nine with tachycardia) ($p=0.82$). In patients with adequate peri-ictal respiratory data, two of seven in the SUDEP group and six of 35 controls had disordered breathing ($p=0.49$). In the SUDEP group, both had agonal breathing. In the controls, five of six had agonal breathing, three of whom also had hypoxemia with oxygen saturation nadirs of 67%, 83% and 86%. The patient with the oxygen saturation nadir of 86% was in non convulsive status epilepticus during this time interval. One individual had hypoxemia with oxygen desaturations <50% without agonal breathing.

DISCUSSION

Our findings demonstrate that neither the revised SUDEP-7 Inventory score nor the cumulative presence of independent SUDEP risk factors identified by a large combined analysis could reliably distinguish individuals dying of SUDEP from living epilepsy patient controls. Further, proposed physiological biomarkers of SUDEP risk, including PGES, peri-ictal cardiorespiratory dysfunction, and HRV were not significantly different between the two groups.

Large scale epidemiological data has improved our understanding of SUDEP risk in the general epilepsy population. However, attempts to focus individual risk stratification measures using these data, such as the SUDEP-7 Inventory, appear to fall short. The SUDEP-7 Inventory has not been clinically validated as a SUDEP predictor, and it is unknown what any given score indicates in terms of individual SUDEP risk. In our study, SUDEP-7 Inventory scores were not predictive of SUDEP. Though not a statistically significant finding, the range of scores was higher in controls than SUDEP cases, and two SUDEP victims had scores of 0. It does not appear, therefore, that this scale can be used alone as an indicator of individual SUDEP risk.

Studies examining potential SUDEP biomarkers using the SUDEP-7 Inventory as a risk marker must therefore be interpreted with caution.^{6, 7, 8} Prolonged PGES is considered a marker of SUDEP risk,¹¹ though this has not been replicable across studies.¹³ The ubiquity of this finding with FBTCS suggests it is more likely an epiphenomenon rather than a distinct biomarker of a rare event such as SUDEP. In our series, when considering all recorded seizures, PGES was more common in the SUDEP group. However, when taking only FBTCS into account, the difference was no longer significant. Other measures, such as peri-ictal cardiorespiratory dysfunction or inter-ictal HRV are of uncertain relationship to SUDEP. Despite these measures correlating with SUDEP risk, as indicated by SUDEP-7 Inventory scores in other studies, they were not more commonly observed in SUDEP cases over controls in our study.

One possible explanation for our negative findings is that the magnitude of risks determined by the large epidemiological studies is too small to apply to particular individuals or small populations. Another possibility is that the cutoffs for defining peri-ictal cardiorespiratory dysfunction, disordered breathing and PGES may have been set too low and more rigorous criteria may have been predictors. However, some of the most severe abnormalities, such as PGES > 50 seconds and oxygen desaturations < 70% were seen in the control group. Furthermore, SUDEP is likely multi factorial, with differing processes playing roles in individual cases. Given the diversity of the epilepsy population, examining small groups may be insufficient to identify trends or statistically significant results. This has substantial implications when counseling individual patients regarding their risk of SUDEP, and for identifying true SUDEP biomarkers.

Limitations of this study include the small sample size and limited available peri-ictal data. Sample size is a common shortfall when studying relatively rare conditions such as SUDEP. Seizures were not recorded in all subjects, which limits drawing specific conclusions or

making comparisons to prior series^{11, 13} for peri-ictal findings such as PGES. Multicenter collaborations, such as the NIH-funded Center for SUDEP Research, aim to mitigate these limitations.¹⁴ Secondly, we selected matched controls based on age, gender, and epilepsy syndrome. Gender is a potential confounder for the ILAE score, while age, and thereby epilepsy duration, is a factor in both ILAE and SUDEP-7 Inventory scores. However, the range of risk factors was similar for both groups. Finally, while otherwise matched, current living status does not preclude the possibility of future SUDEP, a potential complicating factor in any study using living epilepsy patient controls.

Our findings indicate that our current ability to predict SUDEP risk in individual patients or small populations remains limited, despite increasing epidemiological data and studies of peri-ictal and inter-ictal physiological factors in epilepsy patients. There remains a need for improved understanding of SUDEP pathophysiology and individual risk determination to drive interventions, studies and permit better counseling of individual patients as to their unique SUDEP risk.

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Table 1.

Revised SUDEP-7 Risk Factor Inventory

	SUDEP risk factor definition	Score
1	More than 3 tonic-clonic seizures in last year	0 or 2
2	1 or more tonic-clonic seizures in last year (if risk factor 1 selected, score as 0)	0 or 1
3	1 or more seizures of any type over the last 12 months (if risk factor 4 selected, score as 0)	0 or 1
4	>50 seizures of any type per month over the last 12 months	0 or 2
5	Duration of Epilepsy >=30 years	0 or 3
6	Current use of 3 or more antiepileptic drugs	0 or 1
7	Mental Retardation, I.Q. <70, or too impaired to test	0 or 2

Note: Adapted from Novak JL, Miller PR, Markovic D, et al. Risk Assessment for Sudden Death in Epilepsy: The SUDEP-7 Inventory. *Frontiers in Neurology* 2015; 6:252

Table 2.

Summary of comparison of victims of SUDEP to matched living controls

	SUDEP (16)	CONTROLS (48)	
Gender	8M, 8F	24M, 24F	
Age	42(18-63)	41(10-73)	$p=0.72$
Duration	24(3-48)	21(0.25-45)	$p=0.48$
Epilepsy Type	13(81%) focal 4 (30%) s/p resection 1(6%) generalized 2(13%) Undet	40(83%) focal 6(15%) s/p resection 5(10%) generalized 3(6%) Undet	$p=0.13$
# with >3 FBTCS in last year /# with any FBTCS in last year	3/7	16/32	$p=0.47/p=0.54$
Presence of PGES (#w/FBTCS)	3/6 (3)	5/35 (9)	$p=0.042$ ($p=0.64$)
Mean RMSSD (STD DEV)	23.48 (7.99)	37.29 (22.24)	$p=0.18$
Peri-ictal Arrhythmia	2/6	10/35	$p=0.82$
Disordered Breathing	2/7	6/35	$p=0.49$
SUDEP-7 score	3.3 (0-7)	3.8 (0-9)	$p=0.39$
ILAE score	2.4 (0-4)	2.6 (0-5)	$p=0.62$

M=male, F=female, s/p=status post, Undet=undetermined, w/=with, STD DEV= standard deviation