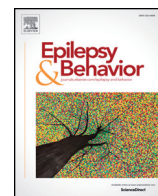




Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Association of sleep with sudden unexpected death in epilepsy

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ARTICLE INFO

Article history:

Received 22 March 2017
 Revised 11 August 2017
 Accepted 14 August 2017
 Available online xxxx

Keywords:

Sleep
 Prone position
 SUDEP
 GTCS

ABSTRACT

Objective: The objective of this study was to determine the association of sleep with sudden unexpected death in epilepsy (SUDEP).

Methods: We conducted a systematic review and meta-analysis based on literature search from databases PubMed, Web of Science, and Scopus using keywords “SUDEP”, or “sudden unexpected death in epilepsy”, or “sudden unexplained death in epilepsy”. Sudden unexpected death in epilepsy was considered to occur during sleep if the patient was found in bed, if the SUDEP cases were documented as in sleep, or if the patient was found at bedside on the bedroom floor.

Results: Circadian pattern was documented in 880 of the 1025 SUDEP cases in 67 studies meeting the inclusion and exclusion criteria. Of the 880 SUDEP cases, 69.3% occurred during sleep and 30.7% occurred during wakefulness. Sudden unexpected death in epilepsy was significantly associated with sleep as compared to wakefulness ($P < 0.001$). In the subgroup of 272 cases in which circadian pattern and age were documented, patients 40 years old or younger were more likely to die in sleep than those older than 40 years (OR: 2.0; 95% CI = 1.0, 3.8; $P = 0.05$). In the subgroup of 114 cases in which both circadian pattern and body position at the time of death were documented, 87.6% (95% CI = 81.1%, 94.2%) of patients who died during sleep were in the prone position, whereas 52.9% (95% CI = 24.7%, 81.1%) of patients who died during wakefulness were in the prone position. Patients with nocturnal seizures were 6.3 times more likely to die in a prone position than those with diurnal seizures (OR: 6.3; 95% CI = 2.0, 19.5; $P = 0.002$).

Conclusions: There is a strong association of SUDEP with sleep, suggesting that sleep is a significant risk factor for SUDEP. Although the risks of SUDEP associated with sleep are unknown and likely multifactorial, the prone position might be an important contributory factor.

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1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is a leading cause of premature death in patients with chronic uncontrolled epilepsy [1,2]. Although the mechanisms of SUDEP remain unclear, it often occurs during sleep, in bed, and unwitnessed. A significant majority (73%) of patients are found in a prone position at the time of death [3,4]. In a case–control study comparing 154 people with definite SUDEP with living controls with epilepsy, those who died were more likely to have a history of nocturnal seizures. Fifty-eight percent of the SUDEP cases were sleep-related, and 86% of the events were unwitnessed [5]. In a seminal retrospective study of mortality in epilepsy monitoring units (MORTEMUS) from 147 epilepsy monitoring units (EMUs) across the world, 14 (87.5%) of the 16 SUDEP cases occurred in the night, and 7 (70%) of the 10 video-EEG-recorded cases occurred during sleep. The body position was documented in 13 of the 16 cases, and patients were exclusively found in prone position [6]. These circumstances of

SUDEP are remarkably similar to those of sudden infant death syndrome (SIDS) and suggest that sleep might be an important risk factor for SUDEP [7,8].

Nevertheless, the occurrence of SUDEP in sleep ranges widely from 25% to 95% among the published case studies [9]. The association of SUDEP with sleep has yet to be determined, and the SUDEP risks associated with sleep remain poorly understood. We, therefore, performed a systemic review and meta-analysis to determine the occurrence of SUDEP during sleep and to further delineate the role of sleep in the pathogenesis of SUDEP.

2. Methods

2.1. Database search

We conducted an extensive literature search from the databases PubMed (1971–2014), Scopus (1971–2014), and Web of Science (1986–2014) using the keywords “SUDEP” or “sudden unexpected death in epilepsy” or “sudden unexplained death in epilepsy.” We also searched by hand the bibliographies of eligible studies for other eligible studies. The searching methods and strategies were formulated under

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the guidance of the medical reference service in the John Crerar Library at the University of Chicago. When necessary, we contacted the authors to clarify study eligibility.

2.2. Inclusion and exclusion criteria

The study inclusion criteria were as follows: (1) publications of one or more possible, probable, and definite SUDEP cases published in the English language; (2) studies that identified if the patient was in sleep or awake at the time of death; and (3) in order to minimize the selection bias, the total number of SUDEP cases with circadian pattern must have been documented. The exclusion criteria were as follows: (1) review articles, editorials, commentaries, animal studies, hypothesis articles, meta-analyses, and letters that reported no new data and (2) small case reports meeting the inclusion criteria, which were later included in larger case series. Sudden unexpected death in epilepsy was defined as sudden, unexpected death in patients with epilepsy, witnessed or unwitnessed, nontraumatic, and nondrowning, excluding status epilepticus or an identifiable cause of death at autopsy. It was considered definite when autopsy revealed no alternative cause of death, whereas it was considered probable when an autopsy was not performed. When there was an alternative cause of death, SUDEP was considered possible [10].

2.3. Data extraction

Two investigators (A.A. and J.X.T.) conducted the database search in unison and reviewed the abstracts and full text articles in duplicates. Disagreements in data extraction were resolved by either consensus or arbitration by a third investigator (S.W.). Cases of SUDEP with documented circadian pattern were identified from the included studies. Additional information was also obtained from subgroups of SUDEP cases, including demographics and circumstances of death such as age, gender, and the body positions at the time of death. We adopted the previously published criteria for asleep and awake states [5]. Sudden unexpected death in epilepsy was considered to occur during sleep if the patient was found in bed, if the SUDEP cases were documented as in sleep, or if the patient was found at bedside on the bedroom floor likely due to falling out of bed during seizures. It was considered to occur during wakefulness if death occurred outside of the bed or bedroom, or if the SUDEP cases were documented as in wakefulness.

2.4. Statistical analysis

Statistical analysis was performed in the Department of Public Health Science at the University of Chicago. Binary random-effects analysis was performed to determine the significance of association between sleep and SUDEP as compared to wakefulness. Chi-square tests were used to compare the difference of circadian pattern at the time of death among the different age groups (age \leq 40 years and age $>$ 40 years), between the genders, and between prone and nonprone positions. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the relative risk of sleep associated with age, gender, and prone position. A forest plot was constructed by calculating the proportion of SUDEP cases during sleep in each study and its 95% CI using a weighted random-effects model. Study heterogeneity (I^2) among the enrolled studies was then determined to assess the study bias.

3. Results

The database searches identified 1357 publications after duplicates were excluded. A review of abstracts for all publications was conducted, and a full text review was conducted in approximately 50% of the publications. Of the 1357 publications, 1280 publications that did not document circadian pattern were excluded; 71 eligible publications

met all inclusion criteria from the database search. Eleven single case reports from the 71 publications were further excluded, as they were subsequently included in large case series that were reviewed. Seven additional publications were found by hand searching the bibliographies of the eligible publications and were enrolled after meeting the inclusion and exclusion criteria. This brought the total number of enrolled studies to 67, consisting of 35 case series and 32 single case reports (Fig. 1).

A total of 1025 SUDEP cases were reported in the 67 studies. A circadian pattern was documented in 880 cases, of which 69.3% (95% CI = 63.0%, 75.6%) occurred during sleep, whereas 30.7% (95% CI = 28.3%, 33.9%) occurred during wakefulness. Binary random-effects analysis showed that SUDEP is significantly associated with sleep as compared to wakefulness ($P < 0.001$) (Fig. 2, Supplementary Table 1). A forest plot was constructed to assess the study heterogeneity (I^2). I^2 reflects the percentage of variance contributed by the study heterogeneity [11]. I^2 was 82.3% in this study and indicated the presence of high heterogeneity, which is consistent with the heterogeneous population of the enrolled studies, varying from single case reports to large case series. For this reason, we adopted a weighted random-effects model to provide a more conservative assessment of the proportion of SUDEP during sleep and its 95% CI (Fig. 3).

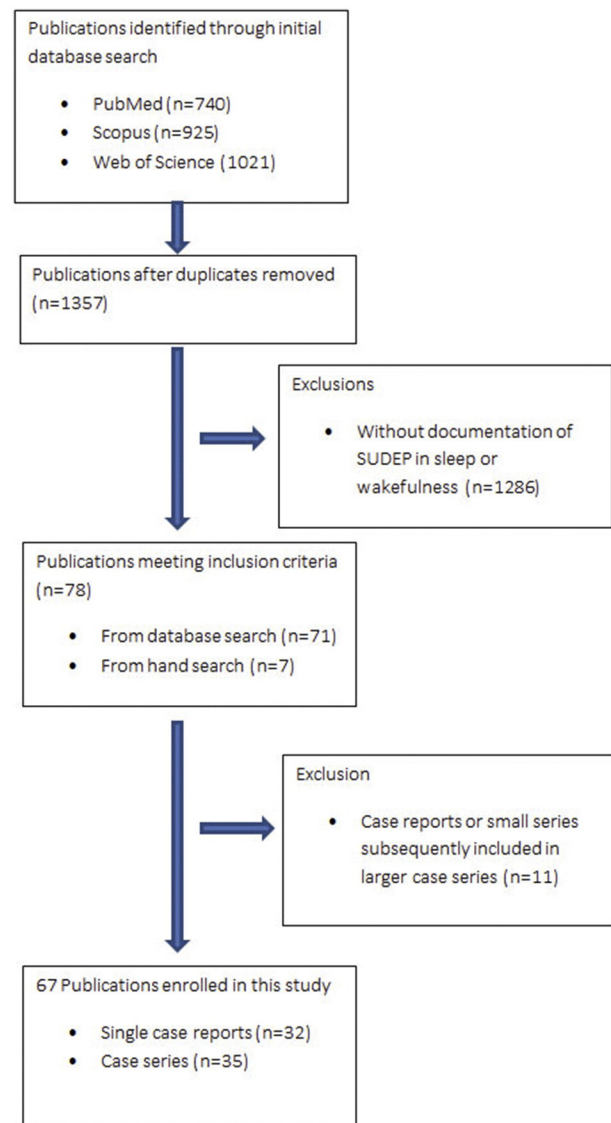


Fig. 1. Search strategy and PRISMA flow diagram.

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