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Original Article

Incidence of sudden unexpected death in nocturnal frontal lobe epilepsy: a cohort study

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ABSTRACT

Objective: Most cases of sudden unexpected death in epilepsy (SUDEP) follow a seizure, and most deaths occur while people are in bed, presumably sleeping. Nocturnal seizures are reported to be a risk factor for SUDEP. People with nocturnal frontal lobe epilepsy (NFLE) have seizures predominantly or exclusively during sleep, often many times per night. The present study aimed to assess whether NFLE represents a high-risk condition for SUDEP.
Methods: The present study retrospectively assessed the incidence of SUDEP in a cohort reconstructed from a dedicated database of consecutive patients referred to the Epilepsy and Sleep Centres of the Institute of Neurological Sciences of Bologna from 1980 to 2012 with: (1) a diagnosis of NFLE, (2) at least 90% of seizures during sleep, and (3) at least one-year of follow-up.
Results: One hundred and three people were included. The median time from seizure onset to last observation was 26 years, equal to a follow-up of 2789 person-years. One person died of SUDEP during the follow-up period. The incidence rate of SUDEP was 0.36 per 1000 person-years (95% CI 0.01 to 2.0).
Conclusions: The incidence of SUDEP in the participant population was not higher than the rates previously reported in prevalent epilepsy populations (0.4 to 2.3 per 1000 person-years). The low prevalence of SUDEP might reflect the low occurrence of generalised tonic-clonic seizures in people with NFLE.

1. Introduction

The pathogenic mechanisms underlying sudden unexpected death in epilepsy (SUDEP) have not yet been unravelled. However, epidemiological studies have pointed to a number of risk factors and precipitating situational circumstances. A terminal seizure appears to be almost universal in the witnessed episodes and when the circumstances of death are reliably recreated [1–8]. Being found dead in bed is very common, especially in a prone position, presumably meaning that deaths occur preferentially during sleep, and the vast majority of the SUDEP cases recorded in video electroencephalography (EEG) monitoring units occurred at night [1,4–10]. Accordingly, a recent study suggested that a history of nocturnal seizures might be an independent risk factor for SUDEP [10].

Nocturnal frontal lobe epilepsy (NFLE) is a syndrome in which seizures occur mostly or exclusively during sleep and tend to be very frequent, occurring up to dozens of times per night [11]. Based on these assumptions, people with NFLE might be at higher risk of SUDEP. The aim of the present study was to assess the incidence of SUDEP retrospectively in a cohort of patients with NFLE, strictly defined as having more than 90% of seizures during sleep.

2. Methods

The present research is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. This retrospective cohort study was part of a larger study designed by the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) of Neurological Sciences (INS) Bologna to investigate the features of NFLE. After approval by the local ethical (cod. 13084)

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committee, the study was conducted from November 2012 to December 2013.

2.1. Data sources

All patients attending the Epilepsy and Sleep Centres of the Institute of Neurological Sciences of Bologna between 1980 and September 2012 for paroxysmal sleep-related events compatible with frontal lobe seizures were progressively screened. The initial pool was partly reconstructed retrospectively by collecting historical, medical and video-polysomnographic (VPSG) records from the database of the Institute. A medical chart recording clinical and instrumental updates at every control visit or telephone/e-mail contact was available for each patient. Control visits in the centres were scheduled on an individual patient basis, depending on clinical needs, with intervals generally ranging from 6 to 12 months.

2.2. Cohort identification and data collection

Patients were eligible if they were diagnosed with NFLE, according to the following criteria: (1) a personal history of motor events arising predominantly from sleep, suggestive of a primary or secondary involvement of frontal lobe structures; (2) video-polysomnographic recording of one hyperkinetic/asymmetric tonic-dystonic episode or at least two stereotyped paroxysmal arousals (PA) [11,13].

Three experts in sleep medicine and epileptology (PT, FP, FB) confirmed the final diagnosis. All cases with VPSG recordings of stereotyped PA that were not associated with major ictal events were carefully reviewed and discussed collegially; the follow-up data were also considered, when available. The agreement required for the final diagnosis was 100%; otherwise these cases were considered doubtful and not included in the study.

Further inclusion criteria were: ≥90% of seizures occurring during sleep and within at least one year of follow-up. The lifetime rate of sleep seizures was independently assessed by BM and LD on the basis of the clinical records; doubtful cases were discussed and cases were only included when there was agreement. All data were retrospectively reviewed until last contact or death. Every effort was made to contact all of the patients who had their last visit prior to 2012 for a telephone interview aimed at verifying their current status and to update clinical information.

2.3. Terminology

Definite, probable and possible cases of SUDEP and SUDEP Plus were defined according to Nashef et al. [14].

2.4. Statistical analysis

The incidence of SUDEP was derived from the total number of people with SUDEP and the total person-year follow-up for the whole cohort. The 95% confidence interval (95% CI) was calculated according to the Poisson distribution.

3. Results

3.1. Population characteristics

In October 2013, the NFLE database contained 165 people. After reviewing the medical charts, 103 were judged to be eligible and included in the study (Fig. 1).

The median time from seizure onset to last observation was 26 years (range 2 to 81 years; mean 27 years; 25th percentile 18 years; 75th percentile 33 years), equal to a follow-up of 2789 person-years, counted from epilepsy onset to last observation/death. Among the people who did not have a check-up in the previous two years, 13 could not be reached by telephone due to a change in number, so their last contact preceded 2012. The median time since seizure onset to last observation in this subgroup was 23 years (range 10 to 39 years).

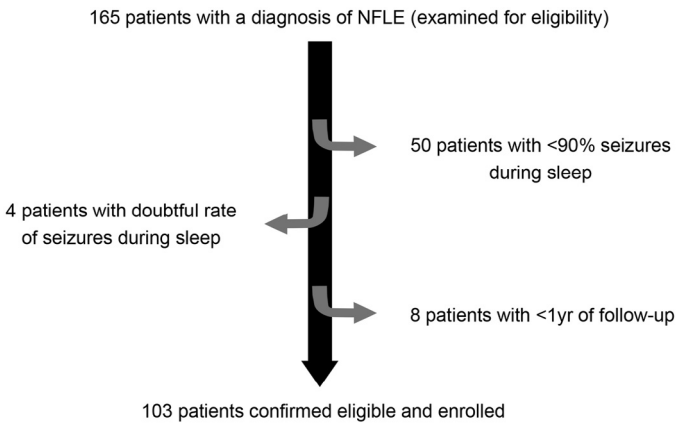

Fig. 1. Flow diagram of the patients with NFLE.

The study cohort comprised 70 males and 33 females. The mean age at onset of epilepsy was 15 years (range 0 to 53). The mean age at last observation was 43 years (range 9 to 86).

The maximum lifetime frequency of seizures was every night for 80 people (77.7%), weekly for 17 (16.5%), monthly for three (2.9%), sporadic for one (1.0%) and unknown for two (1.9%). Frequency of seizures is represented in Fig. 2, as it was at onset (A), at their peak (B) and at last observation (C).

Twenty-nine people (28.1%) experienced secondary generalised tonic-clonic seizures (GTCS). This kind of seizure presented as a unique event or had a sporadic lifetime frequency in 17 people (16.5%), had a maximum lifetime frequency of one or more per year in six people (5.8%), a monthly maximum lifetime frequency in one person (1%), and an unknown maximum frequency in five people (4.8%).

Eight people (7.8%) had obstructive sleep apnoea (OSA), which was considered moderate-to-severe and required continued positive airway pressure (CPAP) treatment in four of them. In the remaining four, OSA was considered to be mild and a weight-loss programme was undertaken.

Eight people (7.8%) refused antiepileptic medication; 39 (37.8%) had been on monotherapy and 56 (54.4%) on polytherapy at some time during their lives. As a first line treatment, they were generally offered carbamazepine once a day, at night. Carbamazepine, alone or in combination, had been taken by 88 people (85.4%). Lamotrigine, alone or in combination, had been taken by 16 people (15.5%).

Ten people (9.7%) underwent a pre-surgical work-up: two subsequently underwent surgery (one removal of a left frontal Taylor dysplasia and the other a frontal corticectomy for an architectural dysplasia), three were judged to be inoperable after the pre-surgical work-up, three refused to undergo surgery or stereo-EEG, one improved significantly with the pharmacological therapy, and in one, the intervention was not performed due to significant surgical risk (see case description below).

A table listing the main characteristics of the people who were excluded because of <90% seizures during sleep is available as a supplementary file (Table 1).

3.2. Mortality rate and incidence of SUDEP

Two people died during the follow-up period. The mortality rate was 0.72 per 1000 person-years (95% CI 0.09 to 2.6). For one, the diagnosis was probable SUDEP (see SUDEP case description below).