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Authors: Alvaro Sanchez-Larsen, Isabel Fernandez-Perez, Alessandro Principe, Miguel Ley, Rodrigo Rocamora



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SUDEP in Spain: first case series and epidemiological analysis

Alvaro Sanchez-Larsen¹, MD; Isabel Fernandez-Perez¹, MD; Alessandro Principe^{1,2}, MD, PhD; Miguel Ley^{1,2}, MD; Rodrigo Rocamora^{1,2}, MD, PhD.

1. Epilepsy Monitoring Unit. Department of Neurology. Hospital del Mar, Barcelona.

2. IMIM (Hospital del Mar Medical Research Institute).

Postal address:

Hospital del Mar: Passeig Marítim de la Barceloneta, 25, 29, 08003 Barcelona. Spain.

IMIM: Carrer del Dr. Aiguader, 88, 08003 Barcelona. Spain.

Corresponding author:

Rodrigo Rocamora, MD, PhD

E-Mail: rocamora@parcdesalutmar.cat

Institution: Servicio de Neurología. Hospital del Mar, Barcelona.

Address: Passeig Marítim nº 25-29. 08003. Barcelona, Spain

Phone number: (+34) 932483727; Fax: (+34) 932483236

E-mails

Alvaro Sanchez Larsen: aa.sanchezlarsen@gmail.com

Isabel Fernandez Perez: 61731@parcdesalutmar.cat

Alessandro Principe: aprincipe@parcdesalutmar.cat

Miguel Ley: MLey@parcdesalutmar.cat

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Highlights:

1. This is the first case series of SUDEP performed in Spain.
2. SUDEP incidence was 1.3 per 1000 patient/year, comprising 0.56% of all deaths.
3. In Spain SUDEP is underdiagnosed and not recognized as a relevant clinical issue.
4. SUDEP risk biomarkers are not consistently assessed in our patients.
5. Health system and administrative issues difficult the register of SUDEP.

Abstract

Purpose: SUDEP is the first cause of mortality related to epilepsy. However, in Spain there are no published cases or series, neither from epilepsy units nor in the general population that could expose the characteristics of SUDEP in our population.

Method: We reviewed all patients treated at our Spanish Epilepsy Reference Centre who died between 2010–2018. SUDEP cases were classified as definite, probable, possible or near-SUDEP. Epilepsy type, demographics and case detection issues were described.

Results: From 1250 evaluated patients, 102 died during the study period. Seven patients were diagnosed with SUDEP or near-SUDEP: two definite SUDEP, one definite SUDEP plus, two probable SUDEP and two near-SUDEP. Specific problems for detection and registration of SUDEP inherent to the Spanish healthcare system and the legal framework were defined. Only 43% of cases were known by the referral neurologist. SUDEP incidence was 1.3 per 1000 patient/year, comprising 0.56% of all deaths in our cohort. Two cases were female, the average age was 36 years (18-61). All patients had focal epilepsy and suffered from generalized tonic-clonic seizures. All witnessed cases occurred after a focal to bilateral tonic-clonic seizure. Four cases occurred during sleep and all non-witnessed cases were found in prone position. One case occurred during video-EEG monitoring.

Conclusions: Our casuistic represents the first case series and epidemiological study of SUDEP cases conducted in Spain. The incidence in our population

agrees with the reported in other countries. However, in our population, SUDEP is probably underdiagnosed due to administrative and legal issues.

Keywords:

SUDEP; near-SUDEP; Spain; epilepsy; mortality; epidemiology; prevalence; incidence.

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Introduction

Worldwide, almost 1% of the population suffers from epilepsy and its annual incidence for all ages is approximately 50 - 55 cases per 100,000 inhabitants [1,2]. In Spain, its age- and sex-adjusted prevalence per 1,000 inhabitants is 14.87 [3]. Epidemiological studies mainly focus on patients with active epilepsy, defined as those who have had at least one seizure in the last 5 years [1]. The incidence of active epilepsy is around 5 - 7.5 per 1,000 inhabitants [1,3-5].

Sudden Unexpected Death in Epilepsy (SUDEP) is the most common epilepsy-related causes of death [6]. It affects approximately 1/1,000 epileptic individuals every year [7] and represents up to 18% of all deaths in these patients [8]. After stroke SUDEP is currently considered the second neurological cause of potential lost years of life [9]. There are different categories of diagnostic accuracy: possible, probable, definite SUDEP, near-SUDEP, and a subcategory "plus" when there is another possible cause of death but its implication has not been established [10]. SUDEP is 23 times more frequent in patients with epilepsy than in the general population [11]. Its incidence varies according to the group of patients analysed: between 0.1 - 2.3 cases per 1,000 individuals/year in all cases; between 1.1 - 5.9 cases per 1,000 individuals/year in patients treated in specialized epilepsy centres, many of whom have drug-resistant epilepsy; and between 6.3 - 9.3 cases per 1,000 individuals/year in epilepsy surgery candidates, or those presenting persistent seizures after surgery [12,13]. European studies have shown a SUDEP incidence of 0.33 to 6.3 per 1,000 patients with epilepsy/year [14-16]. In a recent epidemiological study of epilepsy-

related mortality in a Spanish epilepsy unit, the incidence of definite SUDEP was 0.4 per 1,000 epileptic patients/year of follow-up [17]. However, due to the methodology used, this report offered results similar to those of the general population and not to refractory epilepsies, that is to say, individuals at increased risk.

The objective of our study was to analyse the characteristics of SUDEP and near SUDEP cases diagnosed in a tertiary epilepsy centre in Spain. We aimed to describe the epidemiological features and local constraints with respect to the identification and registering of SUDEP cases in the Spanish health system. To the best of our knowledge, this is the first epidemiological analysis of SUDEP cases reported in a Spanish population.

Methods

Study design

An observational, retrospective study was performed. The publication of this manuscript was in accordance with the Clinical Research Ethics Committee of the IMIM-Hospital del Mar, Barcelona.

Study population:

All patients attended for epilepsy between October 2010 and October 2018 in our Epilepsy Centre (Hospital del Mar, Barcelona) were included. This is a national reference centre (CSUR) for refractory epilepsy, nominated by the Spanish National Health Ministry and part of the European Reference Network (EPI-Care). In our Epilepsy Monitoring Unit (EMU), 24/7 surveillance is provided by trained nurses with exclusive dedication, in addition, an epileptologist is 24/7 on call. We offer specialized care for a reference population of 300,000 inhabitants and receive patients referred throughout Catalonia and Spain. The population base for this study were those patients from the centre who had died during this time period.

Definition of clinical variables

SUDEP was defined according to currently accepted criteria [10]: sudden, unexpected, witnessed/unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with/without evidence for a seizure, and excluding documented *status epilepticus* in which post-mortem examination does not reveal cause of death. Classification was as following [10]: 1) Definite SUDEP: meets all criteria; 2) Probable SUDEP: meets all criteria, but lacks post-mortem data; 3) Possible SUDEP: SUDEP cannot be

ruled out although there is insufficient evidence regarding the circumstances of death and no post-mortem report is available; 4) Near-SUDEP: an epileptic patient survives resuscitation for more than 1 h after a cardiorespiratory arrest that has no identified structural cause; and 5) The previous categories are classified as the subcategory “Plus” when evidence indicates that a pre-existing condition, established before or after the autopsy, could have contributed to death.

Epilepsy is defined as [18]: 1) At least two unprovoked (or reflex) seizures occurring >24 h apart; 2) One unprovoked (or reflex) seizure and a probability of further seizures $\geq 60\%$ occurring over the following 10 years; and 3) Diagnosis of an epilepsy syndrome. The diagnosis of epilepsy in all the study participants was carried out in our outpatient clinic by certified epileptologists and posteriorly reviewed by at least two epileptologists (ASL, AP, ML, and RR). Patients who did not meet these criteria were excluded from the study.

Classification of epilepsies and seizures was performed according to the current guidelines (2017) of the International League Against Epilepsy (ILAE) [19-20].

Assessment of clinical variables

We retrospectively reviewed the electronic clinical records of all patients diagnosed with epilepsy attended in our Epilepsy Centre, either in the outpatient clinics and/or admitted for video-EEG monitoring (VEEGM). The following data were collected from all the participants: age, sex, epilepsy type, aetiology of epilepsy, treatment of epilepsy, and dead/alive status at the time of the review. All causes of death during the study period were evaluated by examining hospital reports, primary health systems, and emergency consultations. When an SUDEP

case was suspected the patient's relatives were requested to respond to a telephone interview in order to ascertain the circumstances. According to the information obtained through the clinical records and the telephone interview, we confirmed or rejected SUDEP diagnosis. The following additional data were collected: age at seizure onset, age at death, family history of epilepsy or sudden death, personal history of seizure-related apnoea, seizure type, seizure frequency for each type in the previous year, and predominance of day/night-time seizures. EEG/video-EEG monitoring recording abnormalities, neuroimaging abnormalities, antiepileptic drug (AED) therapy, epilepsy surgery, comorbidities, comedication, risk factors for seizures (alcohol or other substance abuse, sleep deprivation, poor AED adherence), and the circumstances of death (approximate hour of death, awake or asleep when death occurred, seizure witnessed before death, place of death, situation found). For this study, if the death occurred out-of-hospital and a judicial autopsy was performed, we requested the patient's relatives' permission to obtain the autopsy report through the Institutes of Legal Medicine and the judge responsible for each civil registry. In Spain, the cause of out-of-hospital death is determined by autopsy on the part of the local forensic pathology service. However, this evaluation is only carried out if the cause of death is not clear, depending on the opinion of the physician who completes the death certificate.

Statistical analysis

Descriptive analyses for all variables (means, standard deviation (SD) and frequencies) were evaluated. The proportional mortality for the different causes of death was calculated dividing the number of deaths by the number of patients with epilepsy in our cohort. We calculated the incidence of SUDEP as the number

of SUDEP cases in our cohort during the observation time divided by individual-years at risk. All statistical procedures were performed using the Statistical Package for Social Sciences, Windows (SPSS 22.0. IBM, Chicago, USA).

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Results

The cohort included 1,250 patients whose characteristics are depicted in Table 1. There were 5,203 individual/years follow-up during the study period and 102 participants died. The proportional mortality of the different causes of death is described in Table 2. Seven patients were diagnosed with SUDEP/ near-SUDEP which represented 6.8% of all deaths and affected 0.56% of all the participants. SUDEP incidence in our cohort was 1.3/1000 patients per year. It is notable that only 3 of the 7 cases of SUDEP (43%) were reported to the Epilepsy Unit since they were in the process of active pre-surgical diagnosis. The other 4 were identified only after a retrospective review of clinical records. In none of these cases was the information transmitted from the general practitioner to the reference hospital.

The epidemiological features and comorbidities of the SUDEP patients are described in Table 3. Two patients were female. The average age when SUDEP occurred was 36 years (range 18-61). The mean duration of epilepsy at the time of death was 16.6 years (range 4-51). None of the participants had a personal history of *status epilepticus*, cardiac arrhythmia, or family history of sudden death. One patient (case 7) had previously presented post-ictal apnoea. All the subjects suffered from focal epilepsy. Four cases had temporal lobe epilepsy, two frontal lobe epilepsy, and one posterior quadrant epilepsy. The aetiology of epilepsy was structural in 3 cases, immune in one case, and unknown in the remaining 3 (Table 3). It is noteworthy that some characteristics were shared by all seven patients including refractory focal to bilateral tonic-clonic seizures (FBTCS), the most frequent seizure type in all cases. All patients had at least one seizure per month whilst five (71%) suffered more than one. All of them presented nocturnal

seizures but only one case evidenced a predominance of such distribution (Table 3).

The AEDs used at the moment of SUDEP are described in Table 3, and factors of adherence and/or past reported AED low levels in Table 4. Two patients were on monotherapy, two received two AED, and the other three were under polytherapy with more than two AED. We reviewed the blood AED levels evaluated during recent years in our SUDEP patients and found results for patients 3, 5, 6, and 7. Patient 3 had normal blood levels of valproate acid (VPA) and phenobarbital (PB) in a blood test six months prior to SUDEP. Patients 5 and 6 had normal VPA levels a year before SUDEP took place. Patient 7 had several levels of VPA below the therapeutic range in routine exams in the past although the latest was within the normal range. In addition, we checked our electronic records and confirmed that in 6 out of 7 cases there were clear reports of poor adherence to treatment.

Six patients (86%) had definite drug-resistant epilepsy and two were considered appropriate candidates for epilepsy surgery (Table 3). In case 5 a selective amygdalohippocampectomy on the basis of hippocampal sclerosis (confirmed by anatomopathological examination) was performed, but seizures persisted. Due to a behavioural disorder an invasive study was excluded, and subsequently the subject underwent a second surgery by means of an anterior temporal lobectomy. Nevertheless, seizures continued suggesting the possibility of an insular epilepsy. SUDEP took place three months after the second surgery. Case 4 was on the waiting list for epilepsy surgery when SUDEP occurred. In four patients a pre-surgical study was started (57%). No autonomic features were observed in the clinical semiology review of recorded seizures. The ECG analysis

during the recorded seizures showed: no changes in auras, mild sinus tachycardia (below 95 bpm in all cases) in focal impaired awareness seizures, and marked sinus tachycardia when focal seizures evolved to bilateral tonic-clonic seizures. In case 4, after a FBTCS some supraventricular extrasystoles, and a single ventricular extrasystole could be observed lasting for 1 minute. Case 7 occurred during a VEEGM. AED were completely discontinued when cardiorespiratory arrest (CRA) took place. Seizure commenced in the left posterior quadrant and evolved to a FBTCS. Subsequently, a prolonged (8 minutes) post-ictal generalized electroencephalographic suppression (PGES) was observed (Figure 1). In the early post-ictal, respiratory rate was 12 rpm, followed by a terminal apnoea 39 seconds after seizure end. Heart rate persisted 2 minutes after seizure end, but dramatically dropped after that time, leading subsequently to asystole. Cardiopulmonary resuscitation (CPR) was started within the first minute after asystole, and spontaneous breathing and heartbeat were recovered after 2 min of CPR without consequences. No other respiratory dysfunctions during or after seizures were observed in the other SUDEP patients.

Factors related to death are shown in Table 4. Death occurred during sleep in 4 cases (57%). Three of them slept alone and were found dead by relatives in prone position and abnormal position in bed; case 4 showed a tongue bite and enuresis, suggesting that a seizure had probably occurred before decease. Remarkably, all the non-witnessed cases of SUDEP were found in prone position. In all witnessed cases cardiorespiratory arrest (CRA) occurred after a FBTCS (Table 4). Case 7 occurred in the EMU and CPR administered by sanitary personnel. In cases 2 and 6 a CPR was started by the witnesses and continued by the emergency team, being effective in case 6, but not in case 2. Unfortunately, in

the latter the time in asystole was prolonged, and after 72 hours the patient was diagnosed with brain death due to severe anoxic brain injury. Patients 6 and 7 met the criteria of near-SUDEP (Table 4). Five patients (71%) revealed risk factors for uncontrolled seizures: in one case AED therapy was discontinued during VEEGM, three cases showed poor treatment adherence (case 3 had infra-therapeutic AED levels in the autopsy toxicologic test), and in two cases recreational drug abuse was confirmed (Table 4).

Only in 4 cases (57%) was an autopsy performed; the results are summarized in Table 4. In all SUDEP cases, the patient's relatives responded to the telephone interview, but in case 1 the local court responsible for the case refused to provide the autopsy report. In case 6 the family turned down the necropsy, but during admission a complete study had been performed, ruling out other causes for CRA apart from the previous seizure. None of the performed autopsies revealed a cause for the deaths, and in none was SUDEP mentioned as a possible diagnosis, although in all cases the pathologist knew the antecedent of epilepsy. It is noteworthy that in all cases congestive pulmonary oedema was described, as well as abundant secretions in the upper airways. Case 4 had a 75% stenosis of the anterior descending artery, considered asymptomatic since no myocardial infarct was found. In summary, 2 patients presented definite SUDEP, 1 definite SUDEP plus, 2 probable SUDEP, and 2 near-SUDEP.

Discussion

We reviewed the causes of death of all patients evaluated for epilepsy in our EMU during the previous eight years. Seven cases met the criteria for SUDEP or near-SUDEP. SUDEP was the only direct epilepsy-related cause of death in our cohort, representing 6.8% of all deaths and affecting 0.56% of the study participants. The incidence of SUDEP was 1.3/1000 patients per year, in agreement with previous studies conducted in multidisciplinary epilepsy units [12,13,15].

SUDEP is the most common epilepsy-related cause of death [6]. Currently, knowledge concerning this issue is increasing among both physicians and the general population. Nevertheless, there is a lack of SUDEP epidemiological studies in southern European countries, probably due to multifactorial causes. For instance, although there was an initiative from the Spanish Society of Neurology to create a national SUDEP registry of SUDEP [21] it did not come into practice. Our study confirms that in our country SUDEP cases are not adequately reported as reflected by the fact that the referring physician was unaware of 57% of cases. Moreover, unless the patients' relatives contacted the referring neurologists (which is quite infrequent [8]) they would not be informed of a case of sudden death. Other observed restrictions included considerable bureaucratic obstacles to obtain autopsy records from courts and medical-legal institutes. This suggests that the Spanish legal system is dissociated from the healthcare structure.

Our analysis supported the importance of several risk factors related to SUDEP. Those present in all our cases were early onset of epilepsy (average, 19.4 years old), poor seizure control, generalized tonic-clonic seizures (GTCS) (0.5-3 per

month), poor adherence to treatment, and long-lasting epilepsy (average 16.6 years), in accordance with previous studies [7,22-26]. The average age at the time of death was 36 years, reinforcing the concept that SUDEP affects mainly young patients [15,27]. Six of our 7 cases (86%) had confirmed poor adherence to treatment, or had presented several low AED levels in routine examinations in the past. In the only patient in whom post-mortem AED levels were available, these were below the therapeutic range, and in case 7 the near-SUDEP episode occurred after AED reduction during VEEGM. Therefore, our data suggest that fluctuations in AED levels may be a relevant risk factor for SUDEP. Data related to the body (posture in bed, enuresis, lingual bite, and sialorrhea) indicated that a seizure probably occurred prior to death. Specifically, mild pulmonary oedema and abundant secretions in the upper airways were present in all the performed autopsies, which are common findings after GTCS [28-30]. In a similar manner, all patients whose death was not witnessed were found in the prone position, which is usual in SUDEP cases [30,31]. However, and this is remarkable, none of the autopsies performed considered SUDEP as a possible diagnosis of death. It is possible that pathologists in our milieu are not familiar with this specific entity.

The final pathophysiological mechanism of SUDEP is far from elucidation. Rather than being associated with a unique common mechanism, SUDEP cases may occur due to the combination of various factors and circumstances at a given moment. The SUDEP cases recorded during VEEGM in the MORTEMUS study [32] revealed cardiac and respiratory dysfunction, altered arousal and PGES pattern, common to all cases. Frequently, after a GTCS there is a period of autonomic dysregulation, initially dominated by a sympathetic hyperactivation coupled with parasympathetic suppression, while the later phase is characterized

by an impaired vagal recovery [33]. The PGES pattern correlates with baro- and chemoreceptor centre dysfunction, the production of central apnoea and cardiac arrhythmias, and it is thought to be an SUDEP risk marker [34]. In our study, 2 of the 4 cases studied with VEEGM had a recorded FBTCS with a PGES pattern (Figure 1). In case 7, near-SUDEP took place during VEEGM, allowing an electro-clinical analysis of the episode. The sequence of events was similar to that most frequently observed in the MORTEMUS study [32]: an early post-ictal neurovegetative breakdown leading to a terminal apnoea that preceded the terminal asystole by 2 minutes. This patient had a documented history of peri-ictal apnoea, which is a proposed SUDEP biomarker [32,34]. SUDEP was more frequent during sleep [35] (57% of our cases), suggesting that different factors associated with sleep (e.g. increased likelihood of being alone or having a non-witnessed seizure, deeper impairment of arousal after seizures, or a five-fold greater risk of PGES [36]) may be determinant for the occurrence of SUDEP.

There is a reported relationship between seizures, cardiac arrhythmias, and cardiac repolarization alterations, especially in the setting of channelopathies [37,38]. Several genetic mutations associated with epilepsy and cardiac repolarization abnormalities have been identified in SUDEP patients (SCN1A, KCNQ1, KCNH2, FBN1, HCN1, SCN4A, SCN5A, EFHC1, NOS1AP, CDKL5, CNTNAP2, GRIN2A, and ADGRV1) [39-44]. One of our patients (case 2) had a previously unknown genetic mutation related to long QT syndrome (LQTS), diagnosed at post-mortem. Two other two patients (cases 5 and 6) had ECG abnormalities (right bundle branch block and left ventricular hypertrophy), and in one case (case 4), supraventricular and ventricular extrasystoles in the early

post-ictal phase were observed. Therefore, in 4 of the 6 accessible ECG recordings some abnormality was determined (Table 3).

Such findings taken together suggest that, in concordance with previous reports, in our case series the pathophysiological risk factors associated with SUDEP were active GTCS, fluctuations in AED levels, seizures during sleep, prone position, male sex, early-onset and long-lasting epilepsy. Moreover, post-ictal neurological depression (represented through PGES pattern) and cardiac conduction abnormalities probably play a crucial role in SUDEP pathophysiological mechanism.

Study limitations:

This study has major limitations. First, there is a selection bias determined by the character of a referral centre. Most of the patients presented hard-to-treat epilepsies and represented a sample from a reference centre, but not of the general population. Moreover, as a monocentric study it additionally suffers from selection bias. Because of the retrospective nature of the study, we cannot rule out the fact that some patients could have been. Finally, the lack of monitoring during most of the SUDEP episodes limits the etiologic and pathophysiologic conclusions that can be obtained from the report.

Conclusions:

This is the first case series and epidemiological analysis of SUDEP cases conducted to date in Spain. Our study suggests that this entity is highly underdiagnosed, a finding that concurs with other authors. Moreover, we confirmed the presence of most the SUDEP risk biomarkers currently described, and established that these biomarkers are not consistently assessed.

Based on this evaluation, we highlighted several characteristics in our health system that might preclude the correct identification of SUDEP. One of them is that this entity may be underappreciated by pathologists leading to an underestimation of final diagnosis of death. In addition, we verified the existence of legal, administrative difficulties to obtain autopsy results, even for the medical specialists responsible for the patient.

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Conflicts of Interest: none

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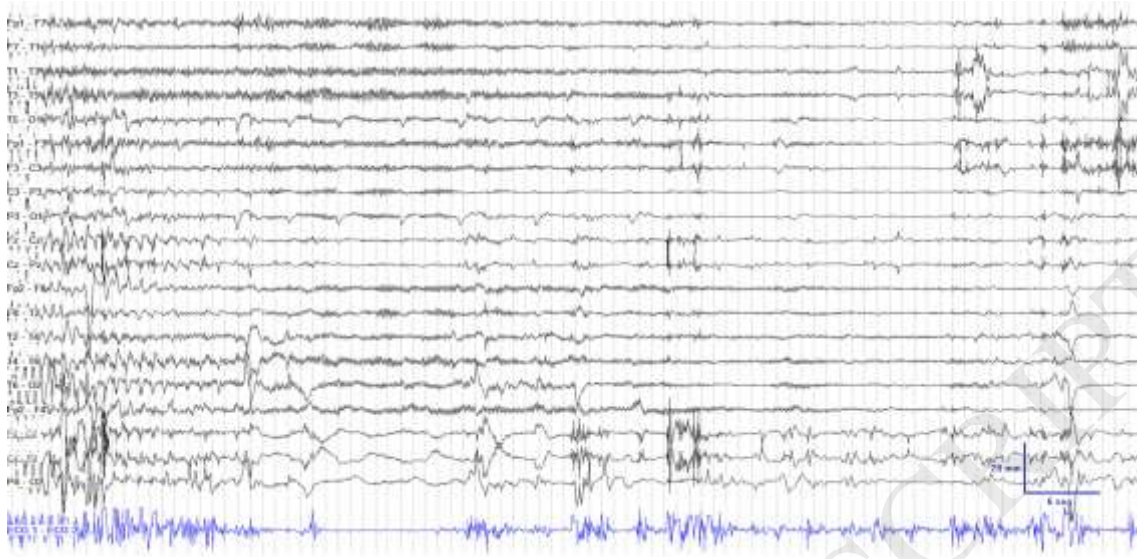
Figures title and legend:

Figure 1. Prolonged post-ictal generalized electroencephalographic suppression after a focal to bilateral tonic-clonic seizures in case 7.

Legend:

Bipolar longitudinal montage. LFF: 1 Hz; HFF: 50 Hz; gain: 10 uV/mm; time-base: 5 mm/seg. Electrode artefacts in C4, P4, and ECG.

Table 1. Characteristics of the study population (n = 1250 patients)

Age	
Mean	48,4 years
Range	3-94 years
Sex	
Male	640 (51.2%)
Female	610 (48,8%)
Epilepsy Type	
Generalized	176 (14.1%)
Focal	796 (63.7%)
• Frontal	250 (20%)
• Temporal	392 (31.4%)
• Parietal	59 (4.7%)
• Occipital	58 (4.7%)
• Insular	7 (0.6%)
• Multifocal	30 (2.4%)
Combined generalized and focal	25 (2%)
Unknown	253 (20.2%)
Epilepsy Aetiology	
Genetic	170 (13.7%)
• CAE	10 (0.8%)
• JAE	14 (1.1%)
• JME	49 (3.9%)
• GTCS only	69 (5.5%)
• Other	28 (2.3%)
Structural	390 (31,3%)
• MTLE with HS	62 (5%)
• MCD	54 (4.3%)
• Brain tumour	72 (5.8%)
• Trauma	61 (5%)
• Vascular malformation	28 (2.2%)
• Perinatal brain injury	37 (3%)
• Stroke/Haemorrhage	55 (4.4%)
• Other	21 (1.7%)
Infectious	21 (1.7%)
Metabolic	2 (0.2%)
Immune	3 (0.3%)
Unknown/missing data	664 (51.2%)
Treatment	
Monotherapy	687 (55%)
Bi-therapy	276 (22.1%)
Polytherapy	236 (18.8%)
Other	51 (4.1%)

CAE: childhood absence epilepsy. GTCS: generalized tonic-clonic seizure. HS: hippocampal sclerosis. JAE: juvenile absence epilepsy. JME: juvenile myoclonic epilepsy. MCD: malformation of cortical development. MTLE: mesial temporal lobe epilepsy.

Table 2. Causes of death and proportional mortality in epileptic patients in Hospital del Mar.

Cause of death	Total % (n=102)
Brain tumour	30.4% (31)
<ul style="list-style-type: none"> • Primary brain tumour • Metastatic tumour 	<ul style="list-style-type: none"> • 16.6% (17) • 13.7% (14)
Systemic tumour w/o brain affection	10.8% (11)
Systemic infection	13.7% (14)
Cerebrovascular disease	4.9% (5)
<ul style="list-style-type: none"> • Brain haemorrhage • Ischemic stroke 	<ul style="list-style-type: none"> • 3.9% (4) • 1% (1)
Cardiac causes (non-infectious)	3.9% (4)
Renal causes (non-infectious)	3.9% (4)
Respiratory causes (non-infectious)	3% (3)
Multiorgan failure	8.8% (9)
SUDEP & near-SUDEP	5.9% (6)
Status epilepticus	0% (0)
Other seizure-related causes	0% (0)
Other non-seizure-related causes	14.7% (15)

SUDEP: sudden unexpected death in epilepsy

Table 3. Clinical characteristics of SUDEP and near-SUDEP cases.

ID	Gender	Age (years)	Epilepsy duration (years)	Epilepsy type	Aetiology of epilepsy	Seizure frequency	GTCS	Predominance of nocturnal seizures	Comorbidities	AEDs at SUDEP	Previous AEDs	ECG	Presurgical evaluation	Surgery	Surgical outcome
1	M	34	10	Focal frontal bilateral	Structural: Post-surgical	3/month	Yes	No	Pituitary adenoma, intellectual disability	ZNS, PGB	VPA	Normal	Yes	Not indicated	-
2	F	23	16	Focal temporal unknown	Unknown	1/month	Yes	Yes	Cannabis consumption	LEV	CBZ	Long QT syndrome	No	-	-
3	M	29	11	Focal frontal bilateral	Unknown	9/month	Yes	No	No	VPA, PB, LTG	-	N/a	No	-	-
4	M	35	17	Focal temporal left	Structural: MTS	5/month	Yes	No	No	OXC, CZP	PHT, PB, LEV, VPA, LTG, CLB, ESL	Post-ictal SVES and VES	Yes	On the waiting list	-
5	M	52	51	Focal temporal left	Structural: FCD IIIa	6/month	Yes	No	Meningitis in childhood	VPA, PB, ESL, CLB	PHT, CBZ, LTG, TGB	RBBB	Yes	1 ^o SAH; 2 ^o ATL	Engel III
6	M	18	7	Focal temporal right	Unknown	1/month	Yes	No	Cannabis consumption	VPA	-	LVH	No	-	-
7	F	61	4	Focal posterior quadrant left	Immune	2/month	Yes	No	Hypertension Hypercholesterolemia	LTG, TPM, BRV	LEV, LCS, ESL, CLB, PER, ZNS	Normal	Yes	Not indicated	

AED: antiepileptic drug. ATL: anterior temporal lobectomy. CBZ: carbamazepine. CLB: clobazam. CZP: clonazepam. ESL: eslicarbazepine. FCD: focal cortical dysplasia. GTCS: generalized tonic-clonic seizures. LCS: lacosamide. LEV: levetiracetam. LTG: lamotrigine. LVH: left ventricular hypertrophy. MTS: mesial temporal sclerosis. OXC: oxcarbazepine. PB: phenobarbital. PER: perampanel. PGB: pregabalin. PHT: phenytoin. RBBB: right bundle branch block. SAH: selective amygdalohippocampectomy. SVES: supraventricular extrasystole. TGB: tiagabine. VES: ventricular extrasystole. VPA: sodic valproate. ZNS: zonisamide. N/a: not available.

Table 4. Characteristics of SUDEP / near-SUDEP episodes, autopsy results, and final diagnosis.

ID	Witnessed	Time found (h)	Sleep	Possible Seizure Triggers	Situation found	CPR	Autopsy result	SUDEP
1	No	8-16	Unknown	History of low AED levels	Prone position	No	Unknown	Probable
2	Yes, FBTCs	24-8	Yes	Toxic consumption, Poor adherence	-	Yes, ineffective	Without cause. Mild pulmonary oedema. Long QT-syndrome. Toxicologic: negative for drugs; LEV detected (not quantified)	Definite Plus
3	No	16-24	Yes	Poor adherence	Prone position, abnormal posture	No	Without cause. Mild pulmonary oedema. Mild aortic valve sclerosis. Toxicologic: negative for drugs; PB 9.8mcg/mL, VPA 17.2mcg/mL	Definite
4	No	8-16	Yes	Poor adherence	Prone position, enuresis	No	Without cause. Tongue bite. Mild pulmonary oedema. Asymptomatic 75% stenosis LAD. Toxicologic: negative for drugs; OXC detected (not quantified)	Definite
5	No	24-8	Yes	Poor adherence	Prone position, abnormal posture	No	Not performed	Probable
6	Yes, FBTCs	16-24	No	Toxic consumption, Poor adherence	-	Yes, effective	Not performed	Near-SUDEP
7	Yes, FBTCs	24-8	No	AED stopped for VEEGM	Supine position	Yes, effective	-	Near-SUDEP

AED: antiepileptic drugs. CPR: cardiopulmonary resuscitation. FBTCs: focal to bilateral tonic-clonic seizure. LDA: left anterior descending artery. LEV: levetiracetam. OXC: oxcarbazepine. PB: phenobarbital. SUDEP: sudden unexpected death in epilepsy. VEEGM: video-electroencephalographic monitoring. VPA: sodic valproate.