Case Report

Mortality of all causes and sudden unexplained death in epilepsy (SUDEP) in a cohort of 235 persons living with epilepsy in Rwanda using WHO Verbal Autopsy Questionnaire

Fidèle Sebera [a,b,c], Béni H. Uwacu [a], Wellars Nsanzabaganwa [a], Josiane Umwiringirwa [a], Peter Dedeken [b,d,e,*], Dirk E. Teuwen [b,e], Paul A.J.M. Boon [b]

[a] CARAES Neuro-psychiatric Hospital, Brothers of Charity, Department of Neurology, Ndera, P.O. Box 423, Kigali, Rwanda
[b] Ghent University Hospital, Department of Neurology, Corneel Heymanslaan 10, B-9000 Gent, Belgium
[c] Centre Hospitalier Universitaire, KN3 Avenue, Kigali, Rwanda
[d] Heilig Hart Ziekenhuis, Mechelsestraat 24, B-2500 Lier, Belgium
[e] UCB Pharma, Researchdreef 60, B-1070 Brussels, Belgium

ARTICLE INFO

ABSTRACT

Introduction: Mortality in persons living with epilepsy (PwE) is 1.6–9.3-fold higher than in the general population. Mortality from definite/probable Sudden Unexpected Death in EPilepsy (SUDEP) is estimated at 1.2 per 1000 person-years. We report mortality and SUDEP rate in a cohort of Rwandan PwE.
Methods: PwE presenting for a first visit at the Ndera epilepsy center between January and June 2016 were followed-up prospectively. For PwE who did not attend their follow-up visit, home visits were organized. Deaths were assessed using World Health Organization Verbal Autopsy Standards age-specific questionnaires.
Results: Of 235 PwE enrolled, home visits were organized for 81 (34.4%) PwE who did not return for their follow-up consultation. Seven fatalities (mortality 16.7/1000 patient-years [CI 6.7–34.3]) were recorded (aged 2–80 years). Four had an identified cause. Three were classified as probable SUDEP, resulting in a probable SUDEP rate of 7.1/1000 patient-years (CI 1.47–20.86). Probable SUDEP occurred in PwE (age: 2, 21, 34 years) showing no symptoms of illness while receiving antiepileptic treatment; in two cases, death occurred during sleep.
Conclusion: Although autopsies were absent, the high mortality and probable SUDEP rates warrant future studies to establish causes of epilepsy-related deaths in Rwanda and sub-Saharan Africa.

1. Introduction

Epilepsy is considered the most prevalent neurological condition, and more than 85% of persons living with epilepsy (PwE) live in low-income and low- and middle-income countries (LLMIC) [1]. In 2016, it was estimated that 45.9 million PwE worldwide had active epilepsy and 70 million had lifetime epilepsy [2]. In sub-Saharan Africa (SSA), there is an overall prevalence estimate of active epilepsy and lifetime epilepsy of 9‰ and 16‰, respectively, with modest variation from one subregion to another [3]. Prevalence is twice as high in rural areas as it is in urban settings [3].

Epilepsy is a global public health issue and results – for those affected and their families – in medical, developmental, psychosocial, and economic consequences, which in turn are an important cause of epilepsy-associated poverty. In LLMICs, this increases not only the burden of disease with high numbers of years lived with disability but also years of life lost because of premature mortality [4].

Premature death in PwE in SSA poses an additional challenge. Worldwide, age-standardized mortality rates of epilepsy from unknown or genetic cause were calculated at 1.74 per 100,000 people (specifically, 1.40 for women and 2.09 for men) [2]. PwE living in SSA have the highest standardized mortality ratio, with a median of 5.4 (range 2.6–7.2) [5].

The incidence of Sudden Unexpected Death in EPilepsy (SUDEP) is important [6,7]. In high-income countries, the incidence of definite and/or probable SUDEP among PwE is 1.2 per 1000 person-years (95% CI 0.9–1.5; range 1.1 in PwE <16 years to 1.3 in adults >50 years of

age) [6,8]. Mortality and SUDEP rates in SSA and other LLMIC remain unclear. Definite SUDEP is considered when diagnostic criteria are met and when no other cause of death has been identified through an autopsy or immediate observation surveillance. As autopsies in SSA are very rarely performed, SUDEP is often only reported as probable or possible.

In this report, we describe all-cause mortality and probable SUDEP cases prospectively studied in a cohort of PwE in Rwanda, using the age-specific World Health Organization (WHO) Verbal Autopsy Questionnaire. This tool was designed and validated to assess cause(s) of mortality in the absence of autopsies, which is frequent in LLMIC. The structured questionnaire guides the interviewer during the visit, covering different causes of death and allows additional data from death certificates at town halls or medical files, if available [9].

2. Materials and methods

Between January and June 2016, PwE presenting at the CARAES Neuropsychiatric tertiary hospital (CARAES-NPH) at Ndera (Kigali, Rwanda) were enrolled into an ambispective cohort study only if they presented at the clinic for the first time and had a first seizure or an epilepsy diagnosis of <12 months. Epilepsy was defined as a history of two or more unprovoked seizures [10]. Survival status was assessed by a physical presentation at an out-patient consultation. If a PwE had not returned (lost for follow-up), a home visit was organized to assess the PwE health status.

A multidisciplinary team, including a neurologist, nurse, and research assistant, visited PwE and family at their last known address. Upon verbal consent, the survey, approved by the Ethical Review Board of the CARAES-NPH and Institutional Review Board of the University Teaching Hospital – Kigali (CHU-K), was administered. Survival status verification was completed at 19 months after the enrollment.

When family members reported the death of a PwE, another home visit was conducted. The team interviewed family and/or caregivers using the age-specific World Health Organization (WHO) Verbal Autopsy Questionnaire age-specific questionnaire [9].

2.1. Classification of epilepsy-related deaths

We used the 2016 classification of epilepsy-related deaths with four categories: (*i*) deaths due directly to epilepsy, including SUDEP; (*ii*) deaths due indirectly to epilepsy; (*iii*) deaths due to acute symptomatic seizures; and, (*iv*) deaths due to underlying disease [7].

2.2. Criteria and classification of SUDEP

The SUDEP criteria used were: (*i*) the deceased, before death, had to have had repetitive unprovoked epileptic seizures; (*ii*) death had to have occurred unexpectedly, *i.e.*, in an everyday situation and in people with an otherwise unremarkable state of health; (*iii*) death had to have occurred suddenly, *i.e.*, within minutes (if observed); and (*iv*) there had to be no evidence of any other cause of death, *e.g.*, trauma, drowning, *status epilepticus*, burns, or accident [11,12].

Six categories of SUDEP were considered: (*i*) definite SUDEP if diagnostic criteria were met without evidence of another cause of death through an autopsy or immediate observation surveillance; (*ii*) probable SUDEP if any or all of the criteria described above were met in the absence of an autopsy; (*iii*) possible SUDEP if a competing cause of death was present; (*iv*) near-SUDEP when a PwE had a resuscitation after a respiratory and cardiovascular arrest for which no other cause was found, with the person surviving for up to 1 h; (*v*) no SUDEP if a clear cause of death was known; and, (*vi*) unclassifiable SUDEP when incomplete information did not allow classification [11,12].

3. Results

A total of 235 PwE were followed up prospectively. Based on the medical records, at 19 months after inclusion, attempts to PwE by phone were made and included 81 (34.5%) PwE who did not return for a follow-up consultation. Of these 81 PwE, seven PwE had moved abroad and 74 home visits were organized. Seven PwE could not be traced at their last known address and authorities did not know their new address. The team completed home visits of these PwE and family members of seven deceased PwE.

Out of 35 reasons for loss to follow-up, most frequently reasons cited were lack of insurance/financial means (25.7%), seizure cessation (25.7%), lack of improvement (25.7%) and lack of information/having a normal EEG (14.3%).

At study enrollment, 56% of 235 PwE were male and 70% were <20 years of age (mean 15.6 years, range 0–78 years). Focal-onset including focal to bilateral tonic–clonic seizures (TCS) were present in 12.6% of PwE, whereas unclassified seizures had occurred in 6%. Another 79.4% presented with TCS with unknown onset (and may have included generalized and focal onset seizures), because of limited electroencephalogram and a monthly seizure frequency >10 was reported in 19.6%. Mean age at first seizure and at clinical diagnosis was 10.8 years and 13.4 years, respectively [13].

Clinical features and details of the seven death cases are described in Tables 1 and 2. At baseline, five of seven deaths recorded were male (71.4%), mean age was 31.4 years (range 1–78 years), and six of seven (85.7%) had unknown onset TCS. Three PwE had more than 10 seizures per month, and two had less than two seizures per month.

Based on a total of 420.3 person-years in our cohort, mortality was 16.7 per 1000 person-years (CI 6.7–34.3) conservatively excluding seven PwE who could not be contacted and assumed alive. Four deaths were attributed to specific causes: brain tumor, metastatic liver cancer, head trauma secondary to a seizure, and hypovolemic shock. Of six PwE with known time of first seizure, four had an epilepsy duration of less than five years.

Three cases on AED treatment were classified as probable SUDEP in the absence of trauma or concurrent illness at time of death. The SUDEP rate in this cohort was estimated to be 7.1 per 1000 person-years (CI 1.5–20.9). At the last documented consultation, two of three PwE who had probable SUDEP were seizure-free for 3 months after respectively presenting with between two and five seizures and >10 seizures per month initially. In two SUDEP cases, death occurred during sleep.

4. Discussion

This study reported all-causes mortality and SUDEP rates of a selected PwE population seen at a tertiary referral center [5,6]. Mortality in our cohort was lower than that reported in data from Kenya showing a mortality of 33 per 1000 person-years [14]. In countries with a large epilepsy diagnosis and treatment gap (DTG), epilepsy has an increased incidence of premature mortality [15]. The DTG may increase mortality from all causes, including deaths attributable to lack of access to medical facilities for diagnosis and treatment, *e.g.*, status epilepticus, or preventable causes, *e.g.*, accidents, drowning, head traumas, and burns [15]. In our cohort, the treatment gap may have contributed to mortality as only one death case was on dual treatment and only two PwE were reported seizure-free. Moreover, death registries are often lacking and autopsies not performed; hence, accurate estimation of the occurrence of epilepsy-related mortality in LLMIC can be significantly hampered [16].

The multidisciplinary team proactively organized home visits and interviewed family members and/or caregivers using the validated WHO Verbal Autopsy Questionnaire to understand cause(s) of death, to mitigate for the lack of death or epilepsy registries [9,16].

According to the 2016 classification, four deaths (57.1%) were considered directly attributable to epilepsy (three instances of probable SUDEP and one secondary to head trauma following a seizure); two

Table 1
Demographics and seizure details of PwE with reported death.

Patient	Gender	Age (years)			Seizure	Seizure frequency			Technical investigations		Medication	
		Onset	Inclusion	Death	Classification	At inclusion	At last OPD visit	At death reported by family	EEG	CT/MRI	AED	Concomitant
1	Male	38	40	41.0	Unknown onset, tonic–clonic seizures	<2/mo	<2/mo	Partial seizure control	Normal	No	Carbamazepine	None
2	Female	10	30	31.4	Unknown onset, tonic–clonic seizures	10–30/mo	<2/mo	Partial seizure control	Abnormal[a]	No	Valproic acid, phenobarbital	None
3	Male	25	33	34.5	Unknown onset, tonic–clonic seizures	2–5/mo	3 mo seizure-free	Seizure-free	Unknown	No	Carbamazepine	Haloperidol
4	Male	36	36	37.1	Focal to bilateral seizures	<2/mo	<2/mo	Unknown	Normal	Brain tumor	Valproic acid	Amitriptyline
5	Female	0	1	2.3	Unknown onset, tonic–clonic seizures	10–30/mo	10–30/mo	Partial seizure control	Abnormal[b]	No	Valproic acid	None
6	Male	UNK	78	80.1	Unknown onset, tonic–clonic seizures	5–10/mo	5–10/mo	Partial seizure control	Unknown	Unknown	Phenobarbital	Unknown
7	Male	0	2	2.9	Focal to bilateral seizures	10–30/mo	10–30/mo	Seizure-free	Abnormal[c]	No	Valproic acid	None

AED = antiepileptic drug; CT/MRI = brain computed tomography/magnetic resonance imaging; DoB = date of birth; EEG = electroencephalogram; OPD = outpatient department; UNK, unknown.
[a] Excess delta/theta waves, without epileptic activities.
[b] Theta waves.
[c] Severe encephalopathy.

(28.6%) were the result of underlying neurological disease, and one (14.3%) was related indirectly to epilepsy [5,7,11,12].

The proportion of probable SUDEP of 3/7 (43%) was higher than in the Kenyan cohort (about 7%), which may be due to population differences or to the home visits we conducted [14]. The diagnosis of SUDEP remains difficult in high-income countries and is even more complex and unlikely to be recorded in LLMIC. Risk factors for SUDEP include TCS, high frequency of seizures, nocturnal seizures, polytherapy, non-compliance, age <45 years, and long duration of the condition [17]. In our cohort, the SUDEP risk factors of age <45 years and TCS were present in all cases, and two PwE had a time since seizure onset of more than nine years. In children, brain lesions, male gender, and cognitive or developmental delay are considered additional risk factors [5]. A delayed mental development was observed in the two toddler SUDEP cases.

Having gathered data on mortality and SUDEP cases, the reported rates need to be interpreted with caution as the study (i) was not specifically designed as a mortality study; (ii) had a relatively short follow-up period; and, (iii) potentially selected a population with

Table 2
Narrative and suspected causes of death in seven PwE by using the WHO Verbal Autopsy.

Patient	Health status	Description	Sleep/awake	Infection	GI disease	Cardiac disease	Lung disease	WHO diagnosis
1	Active life	The person was apparently fine, reading at home. At around 03:00 pm, he went outside, had a seizure, fell on some steps, and suffered head trauma. He went to bed, but was later discovered unconscious by family members.	Awake	No	No	No	No	Head trauma, secondary to seizure
2	Active life	At around 03:00 am, the person called out to her mother explaining that she did not feel well. She displayed no signs of fever, pain, or other illness. Having returned to bed to sleep, she passed away during the night.	Asleep	No	No	No	No	Probable SUDEP
3	Active life	At around 03:00 pm, while conducting business, the person told his business partner that he did not feel well. He displayed no signs of fever, pain, depression, paranoid schizophrenia, or other illness. He went home to rest, but after 1 h, his business partner discovered him dead at his home, without apparent injuries.	Asleep	No	No	No	No	Probable SUDEP
4	Deteriorating health	The person, previously diagnosed with a brain tumor, was admitted to the emergency department of CHU-K in a comatose state. He received palliative care but died 5 days later.	Coma	No	No	No	No	Brain tumor
5	Delayed mental development	The medical history of the girl included recurrent infections, requiring nasogastric tube feeding, and supportive care. At time of death, the patient was again admitted with diarrhea, unable to take oral rehydration. She died of a hypovolemic shock despite rehydration with intra-venous fluid.	Awake	No	Diarrhea	No	Respiratory problems	Hypovolemic shock/dehydration
6	Deteriorating health	The person had known lung cancer. His health status deteriorated steadily with a severe cough, chest and abdominal pain, and weight loss. He died in hospital.	Awake	Fever	Abdominal pain	No	Severe cough	Metastatic lung cancer
7	Delayed mental development	The boy with known perinatal asphyxia was apparently fine and did not have seizures at the time of his death. He showed no signs of any illness. At around 11:00 am, he was unable to eat and stopped breathing soon afterwards. No convulsions were observed by household members.	Awake	No	No	No	No	Probable SUDEP

CHU-K = University Teaching Hospital – Kigali; GI = gastrointestinal disease; PwE = person with epilepsy; SUDEP = Sudden Unexplained Death in Epilepsy; WHO = World Health Organization.

likely more severe epilepsy having been referred by district hospital levels. This may have resulted in an overestimation of actual rates compared to the general PwE population as only recently diagnosed PwE were recruited at the tertiary reference center. Similar to other LLMIC, further limitations to assess causes of mortality including SUDEP were an absence of autopsies and limited access to neuroimaging, most likely underestimating brain lesion-related epilepsy [14].

Given these limitations, the WHO Verbal Autopsy Questionnaire was a useful tool for assessing the cause of mortality in a structured and systematic way. We recommend its future use in all instances of deaths of PwE.

Research is ongoing and more is required to improve our understanding of both epilepsy-related mortality and SUDEP rate in Rwanda, and to a broader extent, in SSA.

Ethical statement

The authors confirm that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Where applicable, informed consent from human participants and approval from the appropriate ethical review boards were obtained, as described in the manuscript.

Acknowledgments

Declaration of competing interest

D. Teuwen is an employee of UCB Pharma. P. Dedeken received consultancy fees from UCB Pharma and Novartis. P. Boon received speaker and consultancy fees from UCB Pharma, LivaNova, and Medtronic, and research grants from the same companies through his institution. The other authors have no interests to declare.

Funding disclosure statement

Data statement

Data from non-interventional studies is outside of UCB's data sharing policy and is unavailable for sharing.

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