

Etiology of Sudden Cardiac Arrest in Patients with Epilepsy: Experience of Tertiary Referral Hospital in Sapporo City, Japan

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Abstract

It has been reported that epilepsy patients had higher risk of sudden death than that of the general population. However, in Japan, there is very little literature on the observational research conducted on sudden fatal events in epilepsy. We performed a single-center, retrospective study on all the out-of-hospital cardiac arrest (OHCA) patients treated in our emergency department between 2007 and 2013. Among the OHCA patients, we extracted those with a history of epilepsy and then analyzed the characteristics of the fatal events and the background of epilepsy. From 1,823 OHCA patients, a total of 10 cases were enrolled in our study. The median age was 34 years at the time of the incident [9–52 years; interquartile range (IQR), 24–45]. We determined that half of our cases resulted from external causes of death such as drowning and suffocation and the other half were classified as sudden unexpected death in epilepsy (SUDEP). In addition, asphyxia was implicated as the cause in eight cases. Only the two near-drowning patients were immediately resuscitated, but the remaining eight patients died. The median age of first onset of epilepsy was 12 years (0.5–30; IQR, 3–21), and the median disease duration was 25 years (4–38; IQR, 6–32). Patients with active epilepsy accounted for half of our series and they were undergoing poly anti-epileptic drug therapy. The fatal events related to epilepsy tended to occur in the younger adult by external causes. An appropriate therapeutic intervention and a thorough observation were needed for its prevention.

Key words: cardiac arrest, epilepsy, drowning, suffocation, sudden unexpected death in epilepsy

Introduction

It has been reported that the prevalence of epilepsy (a worldwide disorder) was about 0.8%, the age adjusted prevalence was 2.7–17.6 per 1,000 people,¹⁾ and the number of epileptic patients in Japan is estimated to be between 650,000 and 1 million.²⁾ In children, the prevalence of epilepsy is 0.5–1%,³⁾ and a previous epidemiological study in Japan reported that the rate of incidence was 5.3–8.8 per 1,000 people,⁴⁾ but there is no accurate epidemiological data in our country.

Patients with epilepsy have a mortality rate two to three times higher than that of the general population.^{5,6)}

This high mortality rate is due to causes such as the progression of an underlying disease, epilepsy-related accidents, status epilepticus, aspiration or suffocation during seizure, and sudden unexpected death in epilepsy (SUDEP).^{7–9)}

Even if the relationship between the cause of death and generalized tonic and clonic seizures (GTCSs) is suspected, SUDEP is designated as the cause of death only when an obvious cause (e.g., asphyxia after airway obstruction and drowning during seizure) is not identified. The incidence of SUDEP is reported as 0.9–2.3 per 1,000 person-years, and the rate of sudden death in epilepsy patients is 20 times greater than that of the general population.^{10,11)}

However, in Japan, there is very little literature on the observational research conducted on sudden fatal events in epilepsy. The aim of this study is to analyze the clinical features of out-of-hospital sudden fatal events in patients with epilepsy.

Materials and Methods

I. Study design

The out-of-hospital cardiac arrest (OHCA) patients were identified from the database of Sapporo Medical University Hospital, Department of Advanced Critical Care and Emergency. We performed a retrospective study of OHCA patients from all age groups who were transferred to our department between January 2007 and December 2013. In our database, the subjects were identified using the following keywords: epilepsy, seizure, status epilepticus, or out-of-hospital cardiac arrest. We excluded the subjects if there was obvious evidence of trauma or injury. Potential traumatic OHCA patients were excluded from the population because we were unable to determine whether the onset of the injury occurred after ictus epilepticus or if it was the result of an accident. These traumatic cases also included intentional injury such as suicide.

II. Data sources

The population of the city of Sapporo is approximately 1,914,000. Our hospital is one of the five major tertiary care centers that handle approximately 90% of out-of-hospital cardiac arrest cases in the city. For all calls involving cardiac arrest, patients are transferred to the nearest of the five major tertiary care centers. In the city of Sapporo, all 9,553 patients with OHCA were transported to one of the tertiary care centers; 2,249 OHCA people were transported to our facility. Among the epilepsy patients transported to our department due to OHCA, we retrospectively investigated the conditions of the arrest, the clinical features of the event, and the patient's background of epilepsy. Data subjects were age on admission, gender, time at which OHCA was recorded (24 h), location (public or private space), asphyxiation event (yes = y/no = n), witness of collapse (y/n), and an epileptic convulsion (y/n), electrocardiogram (ECG) findings first documented at the scene [pulseless ventricular tachycardia (VT), ventricular fibrillation (VF), pulseless electrical activity (PEA), and asystole], the presence of a return of spontaneous circulation (ROSC) (y/n), therapeutic intervention during resuscitation, outcome at hospital discharge (CPC; cerebral performance category: CPC 1, a return to normal cerebral function or with only slight disability; CPC 2, alert with moderate disability; CPC 3, conscious with severe disability; CPC 4, comatose or in a

persistent vegetative state; and CPC 5, brain death or dead), and cause of OHCA estimated from the description of the medical record. The generation-specific proportion of epilepsy-related OHCA was examined: 0–40 years (children and younger adults), 41–65 years (adults), and more than 66 years (elderly).

In our study, the causes of death were defined as follows: “drowning” was defined as death by asphyxia due to submersion in a liquid medium and “near-drowning” was defined as immediate survival after asphyxia due to submersion. In cases in which gastric contents were removed from the airway by the first responder or emergency medical service (EMS), the cause of CA could be defined based on the degree of airway obstruction correlated with mortality. “Suffocation” was defined as complete airway obstruction.

SUDEP classification in this study was based on the guidelines proposed by Nashef et al. (Table 1).¹²⁾ As our study did not include any cases for which postmortem examinations were performed, a case for which the cause of death could be not identified was diagnosed as “probable SUDEP.” It was referred to as “possible SUDEP” in cases of incomplete obstruction by an oral foreign body. The case that survived resuscitation for more than 1 h after a cardiorespiratory arrest was defined as “near SUDEP” regardless of postmortem examination findings. In addition, a history of epilepsy, which included age at first onset, disease duration, neurological deficit including mental retardation, cognitive disorder, type of epilepsy (generalized, focal, unclassified), diagnosis of epilepsy (including probable diagnosis), name and number of anti-epileptic drug (AED), additional oral anti-psychotic drugs (y/n), last frequency of generalized tonic and clonic seizures (per year), the frequency of simple partial seizures (SPSs) and complex partial seizures (CPSs) including the secondary generalized ictus (per month), previous electroencephalogram (EEG) findings, and primary clinical department, was investigated retrospectively. If some of the data points were not included in the medical records, we requested more information from the family physician to create as accurate a description as possible.

III. Ethics approval

This study was performed with the approval from the research ethics committee of Sapporo Medical University. We obtained the acceptance and patient referral documents from primary hospitals or institutions advising us to disclose only the data necessary to our study and to not disclose either personal information of any patient or items that the hospital did not wish to be disclosed regarding medical care information (e.g., official medical charts). We were unable to obtain informed consent from the patients

Table 1 Proposed unified sudden unexpected death in epilepsy (SUDEP) definition and classification, modified from the table from Ref 12

Classification	Definition
1. Definite SUDEP	Satisfying the definition of definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death
2. Probable SUDEP	Same as definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death
3. Possible SUDEP	A competing cause of death is present, otherwise healthy patient with uncontrolled epilepsy; found dead in the daytime; postmortem examination reveals aspiration of gastric contents of unspecified amount. Drowning would have excluded SUDEP, but postmortem examination does not exclude dry drowning. There is a competing cause for death; thus, possible SUDEP. Unspecified amount of aspirated substance does not allow for determination of SUDEP. Minor aspiration is consistent with SUDEP, but severe aspiration itself is a cause of death
4. Near SUDEP	A patient with epilepsy survives resuscitation for more than 1 h after a cardiorespiratory arrest that has no structural cause identified after investigation
5. Not SUDEP	A clear cause of death is known
6. Unclassified	Incomplete information available; not possible to classify

and their families because most of the patients were deceased, except in the case of one individual and his or her family.

Results

Two thousand two-hundred and forty-nine OHCA people were transported to our facility, from which we identified 1,823 patients that satisfied the entry criteria. Among them, there were 10 OHCA patients with epilepsy who had been transported to our facility. The generation-specific proportion of epilepsy-related OHCA was as follows: 0–40 years (children and younger adults) 6% (6 out of 93 cases), 41–65 years (adults) 1% (4 out of 460 cases), and more than 66 years (elderly) 0% (0 out of 1,270 cases).

I. Characteristics and outcomes

The background information of the 10 cases is shown in Table 2. The median age was 34 years at the time of the incident [9–52 years; interquartile range (IQR), 24–45], and there were six male and four female cases. Regarding the cause of OHCA, 3 of the 10 patients were classified as suffocation victims, 2 as drowning victims, and 5 as SUDEP cases. Asphyxiation events after airway obstruction and drowning were implicated as the cause of events in eight cases.

In the three “suffocation” cases (case 1, 2, and 3), complete airway obstruction due to gastric contents was observed, which was confirmed in the medical documentation recorded by EMS.

In four cases, submersion of the face or body occurred in either a public pool ($n = 1$) or bathtub ($n = 3$). Two “drowning” cases (case 4 and 5), in which the individuals were discovered submerged in the home bathtub, had diffuse lung fields with an infiltration shadow in the chest X-ray findings, which is consistent with drowning.

Clinical courses of five SUDEP cases are described as below. Two “near-drowning” patients (case 6 and 7) in a public space (one in a public bath and one in a public pool) were immediately resuscitated by the first responder or EMS, and achieved ROSC before arrival at the hospital. The chest X-ray showed only a mild infiltration shadow via aspiration, which was not identified as severe pulmonary edema. These two cases were discharged from the hospital without new neurological deficits. These near-drowning cases were defined as “near SUDEP.” But other three SUDEP cases that showed “asystole” on their initial cardiac rhythm died after all. Although ictus-related events were witnessed in two of latter three cases, successful resuscitation was not achieved. A 25-year-old male (case 8) was found suffering from cardiac arrest (CA) in a restroom in a home. No oral vomit was detected by EMS. Although ROSC was achieved in the emergency room (ER), he died 11 h after ICU admission. Hypoxic encephalopathy was observed in a head computed tomography (CT), and there was no noticeable appearance of neurologic improvement. An autopsy was not performed. There was no obvious abnormality caused by CA revealed by the laboratory analysis, other radiological

Table 2 Patient presentation, conditions of out-of-cardiac arrest, and clinical outcome

Case No	Time		Location of event		Asphyxiation event	Witness		ECG First document	ROSC y/n	Outcome	
	Age	24 h	Home/ Public	Place		y/n	Therapeutic intervention			CPC at discharge	Cause of CA
1	33M	16	H	hall	complete aspiration of gastric contents	y	PEA	n	n	5	suffocation
2	43F	22	H	living room	complete aspiration of gastric contents	n	Asys.	n	n	5	suffocation
3	45F	11	H	kitchen	complete aspiration of gastric contents	n	Asys.	n	n	5	suffocation
4	20M	21	H	bath tub	submersion of the face	n	Asys.	n	n	5	drowning
5	34M	19	H	bath tub	submersion of the face	n	Asys.	n	n	5	drowning
6	9M	17	P	bath tub	submersion of whole body	y	n.d.	y, BLS	y, BLS	1	near SUDEP
7	52F	17	P	pool	submersion of whole body	y	n.d.	y, BLS	y, BLS	1	near SUDEP
8	25M	8	H	toilet	n	n	Asys.	y, epi 3 mg	n	5	probable SUDEP
9	34M	2	H	bedroom during sleep	n	y seizure	Asys.	n	n	5	possible SUDEP
10	45F	10	H	living room	incomplete aspirating gastric contents	y seizure	Asys.	y, epi 2 mg	n	5	possible SUDEP

Asys.: asystole, BLS: basic life support, CPC: cerebral performance category, epi: epinephrine, F: female, GCS: Glasgow Coma Scale, M: male, n: no, OHCA: out-of-hospital cardiac arrest, PEA: pulseless electrical activity, ROSC: return of spontaneous circulation, SUDEP: sudden unexpected death in epilepsy, y: yes.

imaging, or ECG findings. Thus, the diagnosis of “near SUDEP” was considered. As for the course of a 34-year-old male (case 9) with temporal lobe epilepsy after viral meningitis, SPS/CPS often occurred during sleep, and his medication dose had been under adjustment. The tachypnea following the 5-minute seizure that occurred during sleep shifted to apnea and then to cardiac arrest. He died after not responding to resuscitation efforts in the ER. Gastric contents and abnormal findings on X-rays were not observed. He was diagnosed with “probable SUDEP.” A 45-year-old woman (case 10) was found in a coma after a 10-minute seizure, and her carotid was not palpable in the ambulance. ROSC was achieved, but she soon re-arrested and died in the ER. The incomplete obstruction by aspiration of gastric contents was observed. Coagulopathy and some infectious etiology were suspected based on the laboratory examination findings, and we considered them triggers for the ictus epilepticus. She was therefore diagnosed as “possible SUDEP.”

Eight of the patients had their first ECG documented by the EMS. They had a higher rate of presentation with asystole ($n = 7$) and PEA ($n = 1$). Interestingly, VF was not observed in any of these cases.

II. History of epilepsy

The details of chronic epilepsy are shown in Table 3. The median age at first onset was 12 years (0.5–30 years; IQR, 3–21), and the median disease duration was 25 years (4–38 years; IQR, 6–32). In terms of epilepsy type, three cases (30%) involved generalized epilepsy, five cases (50%) involved focal epilepsy, one case was unclassified, and the other was unknown. Three cases experienced a GTCS frequency of one or more times per year. An SPS/CPS frequency of two or more times per month was recorded in three cases. Five cases had undergone poly AED therapy, for which the medication had been changed just prior to the event or was being dose-adjusted in two cases, and status unknown (in one case). Seven cases were given sodium channel blocking AEDs such as phenytoin (PHT; $n = 1$), zonisamide (ZNS; $n = 2$), carbamazepine (CBZ; $n = 4$). Neurological deficit including mental retardation was observed in seven cases, including two patients who resided in facilities for the learning disabled. Anti-psychotic drugs had been added in three cases. One patient had undergone vagus nerve stimulation (VNS).

Discussion

The clinical course of our series suggested two characteristics related to clinical issues. First, the fatal events related to epilepsy tended to occur in

the younger adult patients with refractory epilepsy. Second, asphyxiation events after airway obstruction or submersion in water were implicated as the cause of fatal events, including SUDEP cases.

In this study, the peak age of the period for fatal events related to epilepsy was between 20 years and 40 years of age, but there was no fatal event after 66 years. In seven patients, age at first onset was less than 16 years old. It has been reported that epilepsy-related premature death was significantly more likely to occur in young patients with neurological disorders and intractable childhood-onset epilepsy.¹³⁾

Half of the cases died of “suffocation” or “drowning.” Although no seizure before CA was documented in these cases, seizure activity might possibly trigger fatal events. It is inferred that suffocation occurred after ictus epilepticus during meals or bathing. In contrast, the possibility of an accident unrelated to ictus should also be considered. According to a previous report, psychiatric comorbidity played an important role in early mortality in epilepsy.⁸⁾ As patients with cognitive disorders accounted for 70% of our cohort, overeating or carelessness during swimming or bathing might have been related to the fatal event. One of the three cases who died of suffocation had previously experienced an onset of CPS during impulsive overeating. Death by drowning is regarded as a consistently significant cause of death in people with epilepsy.^{14,15)} The risk of drowning in people with epilepsy is much higher than that of the general population, and this increased risk of drowning has not changed over the past three decades.¹⁶⁾ From a large OHCA registry in an urban city of Japan, survival outcomes after OHCA from external causes remains extremely poor in comparison to cardiac origin.¹⁷⁾ The asphyxiation events such as suffocation and drowning may be preventable through the careful observation of people in the vicinity of the victim. An awareness of the surrounding environment and an expanded knowledge of the disorder would both be necessary to achieve this aim.¹⁸⁾

The other half of our series was classified as SUDEP cases. In previous research on SUDEP, cardiac arrhythmia subsequent to ictus as well as either central or obstructive hypoventilation induced by seizure is focused through the autonomic nervous system.^{19–21)} Incomplete asphyxia was implicated as the cause of SUDEP in three of five cases, but we could not confirm the characteristic abnormality in the electrocardiograms that had been taken after resuscitation. Increased risks associated with SUDEP generally involve male patients, a younger age at epilepsy-onset, longer disease duration, mental

Table 3 Clinical features related to a history of chronic epilepsy

Case	Age/ gender (yrs)	Age at onset (yrs)	Disease duration (yrs)	Neurological deficit including mental retardation, cognitive disorder (y/n)	Frequency of ictus		Classification and diagnosis of epilepsy		EEG findings	Time from final ictus (yr/ month)	Anti- psychotic drug (y/n)	AED	
					GTC (n/ yr)	SPS/ CPS (n/ month)	Focal (F)/Generalized (G)	No.				Name	
1	33M	27	6	y, autism spectrum disorder	0	0-1	unknown	unknown	unknown	2 yrs	y	1	CBZ
2	43F	14	29	n	1-2		G	IGE (probable)	unknown	4 months	n	2	ZNS GBP (VPA withdrawal)
3	45F	19	25	n	3≡		G	IGE (probable)	lt. dominant 3-4 Hz poly spike and slow wave complex	1 yr	n	4	VPA CLB PB CBZ
4	20M	0.5	19	y, febrile-induced convulsion	0	0-1	unclassified	severe myoclonic epilepsy in infancy (probable)	diffuse poly spike and slow wave complex	11 yrs	n	1	VPA
5	34M	3	31	y	0-1		F	rt. occipital epilepsy	spike dominant at rt. occipital lobe	3 yrs	n	1	PHT
6	9M	3	6	y, neonatal SAH, non-febrile convulsion	0	0	F	rt. temporal epilepsy	spike dominant at rt. occipital lobe	6 yrs	n	0	-
7	52F	14	38	y	5	5	F	temporal epilepsy	unknown	occurring frequently	y	2	GBP CBZ
8	25M	1.5	24	y, non-febrile convulsion	5	5	F	frontal epilepsy	unknown	occurring frequently	n	4	VPA CBZ TOP LEV
9	34M	30	4	n, viral meningitis	2	2	F	lt. temporal epilepsy	spike dominant at lt. temporal lobe	5 months	n	2	ZNS VPA (dose adjustment)
10	45F	10	35	y	1-2		G	symptomatic generalized epilepsy	unknown	unknown	y	1	VPA

AED: anti-epileptic drug, CBZ: carbamazepine, CLB: clobazam, CPS: complex partial seizure, EEG: electroencephalogram, F: female, F: focal, G: generalized, GBP: gabapentin, GTC: general tonic seizure, IGE: idiopathic generalized epilepsy, LEV: levetiracetam, lt: left, M: male, n: no, PHT: phenytoin, rt: right, SPS: simple partial seizure, TOP: topiramate, VPA: valproic acid, y: yes, ZNS: zonisamide.

retardation, and high frequency of GTCS.^{22,23} Idiopathic epilepsy tends to have a lower risk of SUDEP.¹¹ As for AEDs, it has been reported that polytherapy,²⁴ frequent changes in prescribed doses,²⁵ and sodium channel blockers^{26,27} were associated with the risk of SUDEP. Otherwise, adjunctive AEDs at efficacious doses can provide strong support for successful seizure control, and can contribute to protection against SUDEP in patients with refractory epilepsy.^{28,29} Our cases had some risk factors of SUDEP [focal epilepsy with onset age younger than 16 years old (n = 4), poor seizure control (n = 3), and poly AED therapy (n = 3)]. In our study, we were unable to examine the relationship between AEDs and the potential risk of SUDEP, because ante- or postmortem AED blood concentrations had not been determined in any patient. It is also unclear whether or not efficacious AED treatment was performed just before the fatal event. Therefore, there is the possibility of poor adherence to medical treatment resulting in SUDEP. Furthermore, VNS³⁰ and epilepsy surgery³¹ have been reported to contribute to reducing the mortality risk. In our series, there was no surgical intervention except VNS for one patient. Although it is unclear whether or not our cases had appropriate surgical indications for epilepsy among five focal epilepsy patients, including two cases with intractable temporal lobe epilepsy, the success of surgical treatment could abrogate fatal events.

This study has several limitations. First, we did not have detailed data that could be used for a retrospective study. This is a case series that retrospectively examined 10 cases of epilepsy history records, but other cases associated with epilepsy may have been overlooked. Second, the sudden death of epilepsy patients also contains death irrelevant to ictus epilepticus, because SUDEP may involve a heterogeneous pathology.²³ In our study, there were no postmortem autopsies, but three deaths seemed to indicate SUDEP based on the clinical findings. Third, traumatic OHCA patients were excluded from the population, but trauma deaths associated with epilepsy may also be present in other cases.³² There are a variety of mortality risks such as falls, traffic accidents, poisoning, and suicide attempts that could be classified as an accident.⁹ In our study, SUDEP accounted for half of the cases, which is significantly higher than previously reported,¹¹ because we excluded the fatal cases resulting from either the progression of an underlying chronic disease or obvious trauma from our population parameters.

In our study, the specialty of the primary physicians also varied as follows: psychiatrics (n = 4), neurosurgery (n = 2), neurology (n = 2), and pediatrics (n = 2). It is necessary to emphasize the importance

of sharing each patient's information as part of a more comprehensive medical care system. All physicians who participate in epilepsy treatment should consistently cooperate with each department, share medical information, and educate patients, families, and the public regarding potential risks such as suffocation and drowning. It is hoped that the results of our study will prove helpful in the treatment of epilepsy.

Conclusion

We retrospectively analyzed OHCA patients with epilepsy in one of the five major tertiary care centers from the city of Sapporo. This study clearly showed that half of fatal events were caused by external causes such as suffocation and drowning, and asphyxiation events after airway obstruction and drowning were implicated as the cause in most cases. The fatal events related to epilepsy readily occurred in the younger adult groups, and successful resuscitation was very low. Further studies involving more patients and multi centers are needed to verify our findings.

Conflicts of Interest Disclosure

The authors declare no conflict of interest. Their contributions to the study and manuscript preparation are as follows: K. Miyata drafted the manuscript. S. Ochi, R. Enatsu, K. Tanno, S. Uemura, H. Inoue, and K. Maekawa supervised and participated in the evaluation and helped to draft the manuscript. K. Usui, E. Narimatsu, N. Mikuni, and M. Mizobuchi supervised the evaluation and edited the manuscript. All authors read and approved the final manuscript.

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