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SUDEP: The First Case Series in Turkey

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ABSTRACT

Introduction: Sudden unexpected death in epilepsy (SUDEP) is defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in whom postmortem examinations do not reveal a toxicological or anatomic cause for death. In this study, data on patients who passed away under observation in the epilepsy clinic due to sudden, unexpected death have been compiled, and we also aim to emphasize the importance of SUDEP in Turkey.

Methods: This study was performed with a total of nine cases. Data were obtained from hospital records, information given by the families of patients, the database of the General Directorate for Civil Services of the Ministry of Internal Affairs of Turkey, and from the Ankara Metropolitan Municipality Cemetery Information System. As the basis of classification and definition, the proposals suggested by Nashef et al., which were made to the International League Against Epilepsy (ILAE) in 2011, were taken into consideration.

Results: Eight of the patients were classified as probable SUDEP and one of them as possible SUDEP; the mean age at SUDEP was 33 years, and the average follow-up period was 19.7 years. In these cases, except for known risk factors (generalized tonic–clonic seizures, nocturnal seizures, severe epilepsy, more frequent seizures, younger age at the onset of epilepsy, unwitnessed seizures, polytherapy, and mental handicap), a different risk factor was not identified

Conclusion: This study is the first case series on SUDEP in Turkey. Postmortem studies are the most important shortcoming of the study. However, the importance of the topic is highlighted by presenting the available data. SUDEP deserves more attention during the daily practice of neurologists, pediatric neurologists, forensic physicians, and family physicians. If death is sudden and unexpected in a patient with epilepsy, SUDEP should be considered, regardless of the clear causes of death.

Keywords: Epilepsy, sudden unexpected death in epilepsy, antiepileptic drugs

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is a source of anxiety for patients with epilepsy who are aware of this and a shocking situation for those who have lost their family members, as this is an unexpected and sudden event, although the incidence rate is low. Many events such as cardiac diseases, traffic accidents, and suffocation may cause sudden and unexpected death; however, when the fact that the risk of sudden and unexpected death is 24 times higher for epilepsy patients than for the general population is taken into consideration, SUDEP should be accepted as an issue to be considered in detail (1,2).

SUDEP in its simplest form is unexpected and sudden death, with or without the presence of a witness, and whether an attack may have occurred during death or not, after the elimination of suffocation, trauma, and status epilepticus in a patient with epilepsy (3). Besides, a structural or toxic reason should not have been found to be the cause of death in postmortem examinations. SUDEP is seen in approximately 0.09/1000 patient-years for patients newly diagnosed with epilepsy, whereas the rate increases to 9/1000 patient-years for those who are candidates for epilepsy surgery (4).

A consensus can be said to have been reached in the definition and classification of SUDEP recently. The first case of SUDEP recorded in the literature was recorded by Bacon and published in the Lancet in 1868, whereas SUDEP was defined for the first time in 1997 by Nashef (3). In 2011, Nashef et al. (5), at a meeting of the International League Against Epilepsy (ILAE), reviewed the definitions of SUDEP and suggested a classification.

Accordingly, SUDEP is divided into six groups.

1. **Definite SUDEP:** sudden, unexpected death occurs in patients with epilepsy whether there is a witness or not, which is not dependent on trauma or suffocation, whether or not there is proof of a seizure and excluding status epilepticus. Besides, there should not be any other cause of death on postmortem examination.

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If there is a situation that is considered to cause death together with SUDEP, which was identified before or after death, this is called "SUDEP Plus." The SUDEP classification is added as a prefix to this term, e.g., Definite SUDEP Plus, Probable SUDEP Plus, etc.

2. **Probable SUDEP:** The same as with Definite SUDEP, but no autopsy is performed.

3. **Possible SUDEP:** There is another factor that competes with SUDEP as the cause of death.

4. **Near SUDEP:** When there is no structural cause in a patient with epilepsy, there arises a need for resuscitation for more than 1 h following cardiorespiratory arrest.

5. **Not SUDEP:** Absence of a clear, definite cause of death in a patient with epilepsy.

6. **Unclassified:** Death of a patient with epilepsy where classification is not possible due to lack of information.

The important risk factors particularly include early-onset epilepsy, young age, male gender, neuropathological structural findings, drug-resistant seizures, generalized tonic–clonic seizures, frequent seizures, nocturnal seizures, abnormal electroencephalogram (EEG) with epileptiform discharges, psychotropic drug use, alcohol or substance abuse treatment, insufficient and rapid changes of drugs, low levels of antiepileptic drugs, and mental retardation (5,6,7).

In this study, data on patients who died due to sudden and unexpected death during clinical follow-up in the Adult Epilepsy Clinic at Hacettepe University Hospitals were compiled and are presented here to draw health workers' attention to the issue of SUDEP.

METHODS

In this study, patients who had SUDEP and are presented here had been followed up for many years in the Adult Epilepsy Clinic at Hacettepe University Hospitals. The data in the files obtained during the follow-up period at the epilepsy clinic formed the basis of this study. We learnt about the death of the patient in three ways: being informed by their families (four cases), when they were called for treatment and examination while waiting for their turn (two cases), or being informed by their relatives when trying to reach the patient using contact information given for scientific research such as genetic surveys (three cases). However, this did not mean that we could reach all the cases. In addition, all the verbal information about death was confirmed by scanning the records of the Ankara province cemeteries (four cases) via the Metropolitan Municipality Cemetery Information System and the remainder via the database of the Turkish Republic Ministry of the Interior General Directorate of Vital Records and Citizenship, and we tried to obtain information regarding the recent history of the patients by contacting their relatives.

The demographic data, seizure classification, epileptic syndrome classification, EEG data, cranial magnetic resonance imaging (MRI) reports, and personal and family histories of the patients were evaluated after being obtained from the file records. In the evaluation of epilepsy surgery, video records from the EEG unit were made use of.

RESULTS

The total number of cases reached during 10 years from 2003 to 2013 was nine. Four of these were females and five were males. The age at the onset of epilepsy was estimated to be 13.8 years on average; the earliest onset of epilepsy was the neonatal period and the latest was at the age of 33 years. The average age of cases at SUDEP was 33 years; the youngest SUDEP case was 24 years of age and the oldest case was 56 years of age. The average period for which the patients were followed up after the diagnosis of epilepsy was 19.7 years; the shortest follow-up period for epilepsy was 8 years and the longest was 36 years. One of the nine cases had left hand dominance. There was a family history of epilepsy in three patients.

When the cases were classified as suggested by the ILAE (5), eight were identified as probable SUDEP and one was identified as possible SUDEP. As no autopsy was performed in these cases, none could be classified as definite SUDEP. The case with possible SUDEP contracted pneumonia during the period before death, and as this could have contributed to death, it was more appropriate to define this patient as a case of possible SUDEP.

EEG records of all the cases were obtained, and cranial MRI assessments were performed. As a result, one case (case no. 3) underwent left temporal lobectomy + amygdalohippocampectomy; another case (case no. 4) underwent a left temporal lesionectomy + amygdalohippocampectomy due to cavernoma. One patient (case no. 6) was meant to undergo a right temporal lobectomy, but the patient died while waiting for the appointment. After preoperative evaluation for epilepsy surgery, it was decided that three patients were unsuitable for resective surgery; two of these were meant to undergo vagal nerve stimulation (VNS), and the third was meant to be controlled with antiepileptic drug treatment. The other cases did not need to be evaluated for epilepsy surgery considering the available radiological, clinical, and electroencephalographic data (Table 1).

In three cases, cranial MRI was reported to be normal; in three other cases, there was pathology on the left, and in the remaining three, bilateral pathology was detected. In the EEG evaluations, epileptiform discharges were recorded in the left temporal region in three cases, in the right temporal region in one case, bitemporally in one case, and generalized activity in three cases (Table 1).

All the cases suffered from generalized tonic–clonic seizures before treatment. Complex partial seizures had been reported in eight cases, whereas simple partial seizures were reported by one patient. However, generalized seizures disappeared during follow-up in all cases. In one case (case no. 8), a psychogenic non-epileptic seizure (PNES) was recorded during long-term video EEG monitoring in addition to generalized seizures (Table 1). It was learnt from the relatives of this patient, hospital doctors, and hospital records that the patient had suddenly collapsed near a hospital while walking along a street during the daytime and he had been taken to the emergency room in a cardiopulmonary arrest situation. He could not be revived and there had been no finding in the examinations to identify the etiology. Unfortunately, no postmortem work had been performed.

All the cases were followed up as drug-resistant epilepsy and many antiepileptic drugs were prescribed. Before death, the patients were on monotherapy or combined therapy with two or three antiepileptic drugs (Table 1).

DISCUSSION

The literature data about SUDEP can be traced back more than 100 years and many studies have been conducted, especially during the last 15 years. In the physiopathology of SUDEP, central sleep apnea, pulmonary edema, systemic acidosis that arises due to seizure-induced acute pulmonary

Table 1. Cases: demographical and clinical data

Case no.	Sex	Age at the onset of epilepsy	SUDEP age	History of epilepsy in the family	Background	Magnetic resonance imaging	EEG	Treatment plan	Seizure type	Seizure frequency	Medication	SUDEP diagnosis
1	Male	16	27	Yes	No feature	Normal	Uninformative	Antiepileptic medication treatment	GTCS, CPS	1–2 times /month	CBZ	Possible SUDEP
2	Female	33	41	None	Premature ovarian insufficiency	Arachnoid cyst at the left temporal fossa	Bilateral epileptiform activity but more prominent in the left temporal region	Died while waiting for video EEG appointment.	GTCS, CPS	1–2 times/day	PRM-OXC-VPA	Possible SUDEP
3	Male	20	56	Yes	Testis CA, operated spinal fracture	Mesial temporal sclerosis at the left hippocampus	Sharp slow waves in the left temporal region	Left temporal lobectomy + amygdalohippo-lobectomy	GTCS, CPS	1–2 times /month	TPM-CBZ-OXC	Possible SUDEP
4	Female	18	27	None	Simple head trauma - 11 years old ITP	Left temporal chronic hemorrhagic cavernoma and developmental anomaly	Left temporal epileptiform activity	Left temporal lesionectomy + amygdalohippo-campectomy	GTCS, CPS	1 time/month	OXC-PRM-LTG	Possible SUDEP
5	Male	13	48	Yes	No feature	Asymmetrical thickening of the righttemporal gyrus (cortical dysplasia?), cerebellar atrophy	Bilateral temporal epileptiform activity	Antiepileptic medication treatment	GTCS, CPS	1 attack during the last 4 years	TPM-OXC	Possible SUDEP
6	Male	12	24	None	Traffic accident–falling from height	Loss of cerebral volume and parenchyma, atrioventricular arrest, hydrocephaly, atrophy of the right hippocampus	Right temporal epileptiform activity	Left temporal lobectomy planned. Died while waiting for operation.	GTCS, SPS	2–3 times /month GTCS, 2–3 times/ mont h SPS	OXC-LTG-TPM	Possible SUDEP
7	Female	0	24	None	Difficult delivery	Infarct sequelae more apparent on the left, encephalomalacia areas	Generalized epileptiform discharges prominent at the frontal electrodes	Died while waiting for VNS operation.	GTCS, CPS	Many CPSs a day and rare GTCS	Clobazam-CBZ	Possible SUDEP .
8	Male	0	29	None	Difficult delivery	Normal	Generalized epileptiform activity	Antiepileptic medication treatment	GTCS PNES	Once every 2–3 months, sometimes PNES	VPA- LTG -TPM	Possible SUDEP
9	Female	13	27	None	No feature	Periventricular nodular heterotopia	Generalized epileptiform activity prominent in the posterior areas	Antiepileptic medication treatment	GTCS, CPS	4-5/day	LTG-CBZ	Possible SUDEP

CA: carcinoma; ITP: idiopathic thrombocytopenic purpura; VNS: vagal nerve stimulation; GTCS: generalized tonic–clonic seizure; CPS: complex partial seizures; SPS: simple partial seizures; PNES: psychogenic non-epileptic seizures; CBZ: carbamazepine; PRM: primidone; OXC: oxcarbamazepine; LTG: lamotrigine; TPM: topiramate; VPA: valproic acid

changes and fatal arrhythmia as a result of this, fatal arrhythmias caused by cardiac autonomic dysfunction induced by seizures on the basis of hereditary cardiac ion channelopathies, and unknown reasons triggered by acute physiological stress are suspected (8). However, as the event is sudden and unexpected and results in death, many opportunities for investigation disappear. Furthermore, in Turkey the number of postmortem examinations that include an autopsy in such cases is much lower than needed. Presenting the available data for the service of science is an important duty for scientists who think that much progress is required regarding this issue. The data of the patients with epilepsy who were followed up by the Adult Epilepsy Clinic at Hacettepe University Hospitals and died of SUDEP were compiled from 2003 to 2013 and found to be worth publishing.

The most important problem in the collection of previous data was accessibility to information on death. It is an important factor to keep robust and productive channels of communication open between the doctor and the patient and patient's family. This will provide the possibility of obtaining feedback about the state of the patient. In this study, the death of three cases was discovered when their family members applied to the epilepsy clinic to give information or declared the death through public communication tools. The death of two cases was discovered while these patients were waiting their turn for treatment and examination, and the death of the remaining four cases was discovered when the patients were called for another scientific survey using the contact information in the patient registry file. Two cases died while they were on the waiting list for investigation with scalp or intracranial electrodes, and another two cases with SUDEP died while they were on the waiting list for the insertion of VNS. It is believed that making advanced examinations of patients who have a high risk for SUDEP quicker by increasing the national standards will decrease the rates of death caused by this situation. However, two cases who underwent epilepsy surgery and were seizure-free on follow-up were also lost due to SUDEP. Therefore, availability for advanced examinations should be created and it should be kept in mind that although everything is done for the treatment of the patient the risk does not disappear totally but is reduced. It has been reported that the risk of SUDEP following epilepsy surgery decreased from 9/1000 patient-years to 6.3/1000 patient-years but still existed (9).

All these data were confirmed by reaching the families of the patients using the registered contact information in the files and later verified from the database of the Turkish Republic Ministry of the Interior, General Directorate of Vital Records and Citizenship and from the Ankara Metropolitan Municipality Cemetery Information System for the patients who died in Ankara. No wrong information was found in the nine cases. The death declaration documents of the four cases buried in Ankara were examined and no notification was found in relation to epilepsy.

In this study, the mean age at SUDEP was identified to be 33. It is stated in the literature that this can be seen at every age but is mostly seen at ages from 20 to 40 (10). Among the risk factors that have been determined for SUDEP, male gender is present. However, during the recent studies, a certain gender bias was not detected (11). Four of the nine cases were females and five were males. The cases were followed up after the diagnosis of epilepsy. The follow-up period was 8 to 36 years and the average follow-up period was 19.7 years. Five of the nine patients experienced seizures at or before the age of 15 and four had a later onset.

All the patients were identified as taking a minimum of one and a maximum of three antiepileptic drugs before death. For some time, antiepileptic drugs such as phenytoin and carbamazepine were suspected of causing SUDEP (12). However, these drugs were understood to play no role in death during recent studies (13).

No postmortem examination or autopsy was performed on the cases, which is the most important drawback of the study. For this reason, no case could be diagnosed with definite SUDEP, according to the classification of SUDEP suggested by the ILAE. However, according to the data obtained from the families of the patients or from the people who had last seen the patients, eight cases were classified as probable SUDEP and one was classified as possible SUDEP. There was no question of intoxication, suicide, or trauma in any of the cases of probable SUDEP. It was predicted that if these cases had undergone a postmortem examination, no pathology would have been found to have caused death and all cases could have been diagnosed with definite SUDEP. In the literature, it is stated that among all the causes of death of epilepsy patients, the percentage of SUDEP is 7%–17% (14), whereas in Turkey, almost no cases of SUDEP have been recorded in the formal records. The rates of postmortem examination are rather low in Turkey.

In conclusion, SUDEP is a condition that should be on the agenda of neurologists, pediatric neurologists, forensic practitioners, and family physicians to a greater extent. Every individual who has been diagnosed with epilepsy and died should be examined for SUDEP if the death was sudden and unexpected, regardless of the clear causes of death.

Epilepsy patients who are followed up should be evaluated regarding this risk factor and those at risk and their families should be informed about SUDEP; however, it should also be considered that information about this situation may cause unnecessary anxiety and misunderstanding for those at a low risk.

It is believed that making advanced examinations in patients who have a high risk for SUDEP quicker by increasing the national standards will decrease the rates of death caused by this situation. Therefore, availability for advanced examinations should be created and it should be kept in mind that although everything is done for the treatment of a patient, the risk does not totally disappear, but it is reduced.

Robust channels of communication between the patient and doctor, providing reassurance to the patient, and recording contact information of the patient's family members are important for getting feedback.

The term "near SUDEP" is believed not to have an exact equivalent in Turkish. The term "near" is English and a synonym of this term is "approximate." For this reason, another Turkish term, which is believed to be more suitable for the situation, has started to be used. When translating some words in the literature into Turkish, we should think of other possible meanings of a term, and sometimes, there may be other words than the first word that come to our minds that might express the original phrase better.

This study is the first retrospective study of SUDEP conducted in Turkey with a series of cases. However, identified cases of SUDEP form the tip of an iceberg. The real figures will be possible to obtain by making declarations of death in a more sensitive way and increasing the rates of postmortem examination, bearing in mind the diagnosis of SUDEP for patients with epilepsy who have died suddenly and unexpectedly.

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