

Implications of Death Certification on Sudden Unexpected Death in Epilepsy (SUDEP) Research

Daniel S. Atherton, Orrin Devinsky, Dale C. Hesdorffer, Cyndi Wright, Gregory G. Davis

ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in individuals with chronic, uncontrolled epilepsy. Epidemiologists use information on death certificates to study SUDEP. Certification of seizure-related deaths varies. Multiple classification schemes have been proposed to categorize SUDEP type deaths. Nashef et al. recently proposed categorizing death into Definite SUDEP, Definite SUDEP Plus, Probable SUDEP, Possible SUDEP, Near-SUDEP, and Not SUDEP. This study analyzes certification of seizure-related deaths by our office and considers how it relates to Nashef's classifications. Investigative reports from 2011-2015 from the archives of the Jefferson County Coroner/Medical Examiner's Office were searched for the terms "seizure(s)" and "epilepsy." Cases (N=61) were categorized as Definite SUDEP (n=13), Definite SUDEP Plus (n=12), Probable SUDEP (n=1), Possible SUDEP (n=2), and Not SUDEP (n=33). The term SUDEP was only used in one case of Definite SUDEP. The other 12 cases were certified with variations of terms "seizure" and "epilepsy." Cases categorized as Definite SUDEP Plus were overwhelmingly certified as deaths due to heart disease. Categories Probable SUDEP or Possible SUDEP comprised three cases, and in one of those a seizure-related term was used on the death certificate. Thirty-three cases were classified as Not SUDEP. The finding that the majority of cases of Definite SUDEP were certified as some variation of "seizure" or "epilepsy" but not "SUDEP" has important implications for SUDEP research. Our study also suggests that cases of Definite SUDEP Plus would be difficult for epidemiologists to identify because cardiovascular diseases are more frequently implicated. *Acad Forensic Pathol.* 2016 6(1): 96-102

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INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in individuals with chronic, uncontrolled epilepsy. The mechanism of death in SUDEP is complicated and of much clinical and scientific interest (1). Recent studies suggest physiologic derangements leading to fatal cardiac arrhythmias or respiratory arrest as a final pathway causing sudden death in these individuals (2-4). Current estimates of SUDEP incidence vary from 0.09 per 1000 patient-years in new-onset epileptics to 9.3 per 1000 patient-years in individuals eligible for epilepsy surgery (5). However, the actual incidence of SUDEP is unknown, and it is likely that the incidence of SUDEP is higher than current estimates.

Due to the sudden nature and often mysterious circumstances of death in SUDEP, many of these deaths are investigated by coroner's or medical examiner's offices who employ medical examiners (MEs)/forensic pathologists (FPs) to examine the bodies of individuals who die suddenly and unexpectedly. Based on the autopsy findings, circumstances surrounding death, and ancillary studies like toxicological findings, MEs subsequently certify these deaths, specifically indicating the cause and manner of death, along with factors that may have contributed to death (6). Death certificates are important sources of information for epidemiologists and public health agencies

that use data from death certificates to determine the incidence of diseases like SUDEP in a population, and also to identify cases for research (7, 8). Forensic pathologists use a wide variety of terminologies when certifying SUDEP and SUDEP-related deaths. A recent survey of FPs on the National Association of Medical Examiner's (NAME) Listserv showed less than half of SUDEP type cases would be identified utilizing ICD-10 (10th revision of The International Statistics Classifications of Diseases and Related Health Problems) epilepsy codes to search death certificates (9).

Classification systems have elsewhere been used to attempt to categorize complex deaths into categories for research and surveillance. The Centers for Disease Control and Prevention created the Sudden Unexpected Infant Death (SUID) Case Registry to standardize the classification of SUID deaths to better track and understand SUID (10). Similarly, multiple clinically relevant classification schemes have been proposed to categorize SUDEP deaths for research (11, 12). Nashef et al. recently proposed a scheme categorizing death into Definite SUDEP, Definite SUDEP Plus, Probable SUDEP, Possible SUDEP, Near-SUDEP, Not SUDEP, and Unclassified (**Table 1**) (13). However, for several reasons, challenges persist in applying these types of classification schemes to death certification. This retrospective study analyzes certification of seizure-related deaths at the Jefferson County Coroner/Medical

Table 1: Nashef's Proposed Definitions of Sudden Unexpected Death in Epilepsy (SUDEP) for Research (13)

Classification	Definition
Definite SUDEP	Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a cause of death
Definite SUDEP Plus	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/recording of terminal event did not prove the concomitant condition to be the cause of death
Probable SUDEP/Probable SUDEP Plus	Same as Definite SUDEP but without autopsy
Possible SUDEP	A competing cause of death is present
Near-SUDEP/Near-SUDEP Plus	A patient with epilepsy survives resuscitation for more than one hour after cardiorespiratory arrest that has no structural cause identified after investigation
Not SUDEP	A clear cause of death is known
Unclassified	Incomplete information available; not possible to classify

Examiner's Office (JCCMEO) and considers how it relates to Nashef's proposed classification scheme.

METHODS

Investigative reports from 2011-2015 from the archives of the JCCMEO were searched for the terms "seizure(s)" or "epilepsy." Cases describing individuals with a history of epilepsy, seizure disorder, or multiple seizures without an indicated etiology were included. Cases were categorized as Definite SUDEP, Definite SUDEP Plus, Probable SUDEP, Possible SUDEP, or Not SUDEP according to the definitions of these categories (**Table 1**). All cases included an investigative report and autopsy, histological, and toxicological findings, except one in which no autopsy was performed. In that case, only the investigative report and toxicological findings were considered in categorizing it.

Cases categorized as Definite SUDEP Plus and Possible SUDEP were generally distinguished based on the perceived and/or indicated medical examiner's interpretation of the case findings as reflected by the case summaries within the autopsy reports and the indicated causes of death. Cases with findings that were interpreted as concomitant conditions were classified as Definite SUDEP Plus, in accordance with Nashef's clinical classification.

Nashef provides multiple possible scenarios of Definite SUDEP Plus including cases involving individuals with known long QT syndrome or coronary artery atheroma, underlying conditions whose presence can leave uncertainty as to their role to death. Of note, cases in which concomitant cardiac conditions were present that could have contributed to death were classified as Definite SUDEP Plus if there was no definitive evidence of myocardial infarction, in accordance with Nashef's scenarios as described. Accordingly, cases of individuals with underlying atheroma and definitive evidence of myocardial infarction would be classified as Not SUDEP. Cases with findings that were clearly interpreted as competing causes of death were classified as Possible SUDEP, in accordance with Nashef's clinical classification (13).

RESULTS

A total of 97 cases were identified searching investigative reports of cases from the JCCMEO archives for the terms "seizure(s)" or "epilepsy" (five with "epilepsy" only; 87 with "seizure(s)" only; and five with both terms). Thirty-six cases were excluded because the individuals did not have a history of seizures; rather, these individuals demonstrated what was described by witnesses as seizure-type activity believed to occur first around the time of death. Of the remaining 61 cases, 13 were classified as Definite SUDEP, 12 as Definite SUDEP Plus, one as Probable SUDEP, two as Possible SUDEP, and 33 as Not SUDEP (**Table 2**).

In only one case of those categorized as Definite SUDEP was the term SUDEP used on the death certificate. Variations of terms related to "seizure" or "epilepsy" were used in all the other 12 cases. In only one case of those categorized as Definite SUDEP Plus was any seizure-related term mentioned on the death certificate. Cases categorized as Definite SUDEP Plus were most commonly (8/12) certified as deaths due to heart disease (atherosclerotic coronary artery disease or hypertensive heart disease). For cases categorized as Probable SUDEP or Possible SUDEP, only one case had a seizure-related term mentioned on a death certificate (**Table 2**). Accidental drug toxicity was implicated on the death certificates for the majority of deaths categorized as Not SUDEP.

DISCUSSION

This study applies Nashef's classification scheme to relevant medical examiner cases at the JCCMEO with completed death certificates. The majority of Definite SUDEP cases were certified as some variation of "seizure" or "epilepsy" but not SUDEP. Since MEs are not typically using the term SUDEP on death certificates, it would not be possible for epidemiologists to identify most SUDEP cases. In a study of 74 deaths that met the generally accepted definition of SUDEP at the Office of the Chief Medical Examiner (OCME) in Baltimore, Zhuo et al. reported that in only eight cases was SUDEP listed on the death certificate (14). Reasons for this vary. Death certificates have multiple

Table 2: Nashef's Clinical Classifications of Sudden Unexpected Death in Epilepsy (SUDEP) Applied to Medical Examiners' Cases at the Jefferson County Coroner/Medical Examiner's Office (JCCMEO)

Nashef's Clinical Classifications (JCCMEO Cases)	Causes of Death (Contributing Factors)	Manners of Death
Definite SUDEP (13)	Sudden unexplained death in epilepsy (SUDEP)	Natural
	Epilepsy	Natural
	Seizure/epilepsy	Natural
	Probable complication of seizure disorder	Natural
	Seizure disorder	Natural
	Probable seizure/complications of hypoxic brain injury at birth	Natural
	Epilepsy	Natural
	Sequelae secondary to seizure episode	Natural
	Seizure disorder	Natural
	Seizure disorder	Natural
	Complications of epilepsy	Natural
	Complications of epilepsy	Natural
	Asphyxia/epilepsy	Accident
Definite SUDEP Plus (12)	Seizure disorder (hypertensive heart disease)	Natural
	Coronary artery atherosclerosis (hypertension)	Natural
	Alcoholism	Natural
	Complications of electrolyte imbalance(s)	Natural
	Hypertensive heart disease	Natural
	Coronary artery atherosclerosis (diabetes mellitus)	Natural
	Coronary artery atherosclerosis	Natural
	Severe coronary artery disease	Natural
	Hypertensive heart disease	Natural
	Atherosclerotic coronary artery disease	Natural
	Alcoholism	Natural
Hypertensive heart disease	Natural	
Probable SUDEP (1)	Probable natural causes	Probable Natural
Possible SUDEP (2)	Seizure disorder (bony mid cervical vertebral column fracture)	Accidental
	Undetermined	Undetermined
Not SUDEP (33)	Mostly drug toxicity	Accidents

purposes and audiences. Ideally, the information contained on the death certificate should be adequate for all purposes and audiences, but this is not always, or even usually, the case. The tendency for MEs to certify these type deaths as “seizure” or “epilepsy”-related terms may be related to historical traditions of how MEs code epilepsy-related deaths, as well as consideration of the decedent’s family members and their perceived lack of understanding of medical terms like SUDEP. Patients’ and their families’ education about SUDEP is an issue that has recently received more attention (15-17). Gayatri et al. reported a disparity between clinician’s actual reporting of SUDEP information to parents of children with epilepsy and parents’ expectation of their being informed by clinicians about SUDEP (15), and Friedman et al. reported that United States and Canadian neurologists rarely discuss SUDEP with all epilepsy patients or their caregivers (17). At the time of death it is usually relatives who supply medical history to the death investigator. The more specific the medical information that the family is able to relay the more specifically the forensic pathologist will be able to determine and then certify the cause of death.

Medical examiners usually work with a team of investigators who are responsible for reporting information about a death to the ME, which often includes the immediate circumstances surrounding death, witness/first responder accounts of the events leading to death, scene examination, and information regarding pertinent social and medical history of the decedent, if available. A history of epilepsy or seizures cannot always be established at the time of death, and individuals or family members from whom medical history about a decedent is obtained may or may not be familiar with the details of the decedent’s medical history. In cases where there is a history of epilepsy, this may be overlooked or simply described by family members as a history of seizure activity. In recognition of some of the challenges in death investigation of SUDEP, the North American SUDEP Registry has developed a Field Investigator Epilepsy Deaths Form to help investigators gather information about epilepsy-related deaths for MEs, though this is only currently routinely used in a few jurisdictions (18).

Death investigation in the United States is complex and has significantly evolved over recent decades. However, there are still many jurisdictions where investigation is limited, and MEs receive minimal or no past medical history of decedents. It is very likely that cases of SUDEP are underreported because MEs lack awareness of a decedent’s history of seizures or epilepsy. In the absence of medical records confirming clinically-diagnosed epilepsy, MEs may be hesitant to certify a death as SUDEP. Finally, MEs may not use SUDEP on a death certificate due to unfamiliarity with the term, though in Zhuo et al.’s study of SUDEP cases at the Baltimore Office of the Chief Medical Examiner reported that only two out of 15 medical examiners used SUDEP on death certificates despite 14 of 15 recognizing it as a valid diagnosis (14).

This study also shows that SUDEP or other seizure-related terms tend not to be used on a death certificate if a concomitant condition like cardiovascular disease is identified at autopsy, as has been previously reported (19). Many of these cases would qualify as Definite SUDEP Plus under Nashef’s classification scheme (**Table 2**), and would undoubtedly be of great interest to epidemiologists and researchers, but would never be identified for further study utilizing information found on the death certificates. Definite SUDEP Plus is Nashef’s classification for individuals with a history of epilepsy but for whom a concomitant condition is discovered at autopsy that could have contributed to death. Nashef describes one example of this being an epilepsy patient that suffers cardiopulmonary arrest after a seizure, and postmortem examination shows coronary atheroma, but no evidence of myocardial infarction (13). Twelve cases in this study could potentially be classified as Definite SUDEP Plus, but in only one was any seizure-related term mentioned on the death certificate. Sudden death related to cardiovascular disease was ultimately implicated in the majority of deaths classified as Definite SUDEP Plus.

Complications of cardiovascular disease are the leading cause of death in the United States and worldwide. Death related to cardiovascular disease is easy to establish in a population of individuals with evidence of myocardial infarction or a fatal dysrhythmia

that is discovered or confirmed in a hospital setting. However, sudden cardiac death is more difficult to establish in an ME population due to the lack of gross and histologic findings that definitively prove sudden cardiac death. Often, autopsy only detects significant coronary artery disease or cardiomegaly related to hypertension or some cardiomyopathy, which are well-known conditions that predispose an individual to a fatal dysrhythmia (20). However, it is also well-known that cardiovascular disease including severe coronary artery disease, hypertension, and other causes of cardiomyopathy are ubiquitous in the living population, and why or when some individuals sustain a fatal dysrhythmia due to cardiovascular disease and other individuals do not is often unclear (21). This challenge relates to the concept of probable cause and death certification. While there is often no definitive evidence for a dysrhythmia, MEs often certify a death as being due to some form of cardiovascular disease based on the probability of that being the case given the lack of evidence proving another cause for death. However, it may be possible that a subset of individuals with a history of seizures for which cardiovascular disease is implicated in death instead died of a physiologic derangement associated with SUDEP (22). Our study shows almost as many cases of Definite SUDEP Plus as Definite SUDEP, and it is possible that some cases of Definite SUDEP Plus could have actually been seizure-related deaths. Perhaps an important practical assertion is that, utilizing current death certification practices, few or none of these cases would be identified by researchers for further study because the majority of Definite SUDEP Plus deaths were certified solely as cardiac deaths.

Finally, the effect of ethanol on individuals with epilepsy is another area of interest for epilepsy researchers, as moderate to heavy ethanol intake by individuals with epilepsy is associated with an increased risk for terminal seizure events (23). Search of the JCMEO archives resulted in identification of two cases of individuals with histories of seizures as well as chronic alcoholism, and both of these were certified as deaths due to alcoholism. These cases could potentially be considered for research purposes as Definite SUDEP Plus if alcoholism were interpreted as a concomitant

condition that could have contributed to death, as they were in this study.

CONCLUSION

In conclusion, this study demonstrates some of the challenges public health researchers face in studying SUDEP, specifically by showing how ME cases of SUDEP and SUDEP-related cases apply to Nashef's classification scheme of SUDEP. It ultimately emphasizes the need for collaboration among MEs, clinicians, and epidemiologists toward a certification scheme that is useful for all these groups.

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