

CRITICAL REVIEW AND INVITED COMMENTARY

Unifying the definitions of sudden unexpected death in epilepsy

*Lina Nashef, †Elson L. So, ‡Philippe Ryvlin, and §Torbjörn Tomson

*Department of Neurology, King's College Hospital, London, United Kingdom; †Department of Neurology, Mayo Clinic, Rochester, Minnesota, U.S.A.; ‡TIGER, Lyon Neuroscience Research Center INSERM I028, CNRS 5292, UCBL1 and Hospices Civils de Lyon, Lyon, France; and §Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

SUMMARY

Sudden unexpected death in epilepsy (SUDEP) is a category of death in people with epilepsy occurring in the absence of a known structural cause of death and is most likely heterogeneous with regard to mechanisms and circumstances. SUDEP is particularly difficult to investigate in research studies for several reasons, including its relatively low incidence, its unpredictable occurrence often in unwitnessed settings, and its low rate of complete autopsy examinations. Over the past two decades, two complementary definitions have been used in most SUDEP studies, but often with variations. We propose here a unified SUDEP definition and classification to resolve current ambiguities and to retrieve cases that would not have been further studied if the previous definitions were used. The proposed Unified SUDEP Definition and Classification contains, in addition to concepts inherent in the previous definitions, nine main recommendations. (1) The word “unexpected,” and not the word “unexplained,” should be uniformly used in the term SUDEP. (2) The SUDEP category should be applied when appropriate, whether or not a terminal seizure is known to have occurred. (3) The “Possible SUDEP” category should be used only for cases with competing causes of death, with cases left unclassified when data are insufficient to reasonably permit their classification. (4) Cases that would otherwise fulfill the definition of SUDEP should be designated as

“SUDEP Plus” when evidence indicates that a preexisting condition, known before or after autopsy, could have contributed to the death, which otherwise is classified as SUDEP (e.g., coronary insufficiency with no evidence of myocardial infarction or long-QT syndrome with no documented primary ventricular arrhythmia leading to death). (5) To be considered SUDEP, the death should have occurred within 1 h from the onset of a known terminal event. (6) For status epilepticus as an exclusion criterion for SUDEP, the duration of seizure activity should be 30 min or more. (7) A specific category of SUDEP due to asphyxia should not be designated, the distinction being largely impractical on circumstantial or autopsy evidence, with more than one mechanism likely to be contributory in many cases. (8) Death occurring in water but without circumstantial or autopsy evidence of submersion should be classified as “Possible SUDEP.” If any evidence of submersion is present, the death should not be classified as SUDEP. (9) A category of “Near-SUDEP” should be agreed to include cases in which cardiorespiratory arrest was reversed by resuscitation efforts with subsequent survival for more than 1 h. Scenarios that demonstrate the basis for each SUDEP category are described. If disagreement exists about which category fits a particular case, we suggest the use of consensus decision by a panel of informed reviewers to adjudicate the classification of the case.

KEY WORDS: Epilepsy, Epilepsy mortality, Seizures, Sudden unexpected death in epilepsy.

Sudden unexpected death in epilepsy (SUDEP) is a category of death in people with epilepsy occurring in the absence of a known structural cause of death and is most likely heterogeneous with regard to mechanisms and circumstances. Nonetheless, a definition of SUDEP is needed for reliable ascertainment of incidence, monitoring of trends, comparison between studies, and advancement of

research. In the 1990s, two complementary definitions were published (Boxes 1 and 2) (Annegers, 1997; Nashef, 1997). Since then, these two definitions have been used in most SUDEP studies. The purpose of this article is to revisit, clarify, and unify these definitions, while extending them when necessary. It is not the intention of this article to redefine SUDEP. Our aim is to maintain consistency of the definition with most published research over the last two decades, while allowing for the varying requirements of different research aims in current and future studies. We propose a definition of SUDEP that encompasses the two definitions used to date, which would enable individual researchers to apply SUDEP categories defined by criteria that are appropriate to the objectives of their studies. For example, studies

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Address correspondence to Elson L. So, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, U.S.A. E-mail: eso@mayo.edu

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Box 1. Nashef definition of sudden unexpected death in epilepsy (SUDEP)

Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death.

Adapted from Nashef (1997). Used with permission.

Box 2. Annegers definition of sudden unexpected death in epilepsy (SUDEP)

Criteria for diagnosis of SUDEP

- The victim had epilepsy, defined as recurrent unprovoked seizures
- The victim died unexpectedly while in a reasonable state of health
- The death occurred “suddenly” (in minutes), when known
- The death occurred during normal activities (e.g., in or around bed, at home, at work) and benign circumstances
- An obvious medical cause of death was not found

(Comment: The criteria aimed to exclude accidental deaths due to seizures but included death with or without evidence of a seizure near the time of death.)

Classification of SUDEP

- Definite SUDEP: meets all criteria, with postmortem examination
- Probable SUDEP: meets all criteria, but lacks postmortem data
- Possible SUDEP: SUDEP cannot be ruled out, but there is insufficient evidence regarding the circumstances of the death and no postmortem report available
- Unlikely/Not SUDEP: cause of death clearly established, or the circumstances make SUDEP highly improbable

Adapted from Annegers (1997). Used with permission.

investigating SUDEP mechanisms may select cases in the category of “Definite SUDEP,” whereas other SUDEP categories could also be used for epidemiologic studies.

WHAT’S IN A NAME?

Although the phenomenon of sudden death in epilepsy was mentioned in the literature more than a century ago, it took some time for SUDEP to be emphasized and studied by the scientific community (Terrence et al., 1975; Lathers & Schraeder, 1982; Leestma et al., 1984). The category of sudden death in the general population includes deaths with or without an identified cause. SUDEP refers to sudden deaths in which routine autopsy does not reveal a pathologic or toxicologic cause of death, thus the occasional use of the word “unexplained” instead of “unexpected” in the term *SUDEP* (Earnest et al., 1992; So, 2006). We recommend that the word “unexpected,” and not the word “unexplained,” be uniformly used in the term *SUDEP*. In general, most cases of SUDEP are not totally unexplained, because evidence to date strongly suggests that, in most cases, SUDEP occurs in association with nonstructural pathophysiologic mechanisms from a terminal seizure episode, usually

the generalized convulsive type. Abnormal physiologic or molecular mechanisms underlying SUDEP are anticipated to be more definitively delineated in the future, but their eventual identification as etiologies of sudden death should not preclude those deaths from being defined as SUDEP. Doing so would force research and preventive efforts to “chase” an increasingly narrow group of unexplained sudden deaths in epilepsy, when the ultimate goal of the efforts is to decrease mortality through the correction of causative mechanisms as each is identified. This being the goal, it is appropriate to view SUDEP as a category of sudden death that may have different etiologies. From this perspective, the word “unexpected” would still be suitable when underlying causes or mechanisms are identified in some cases of SUDEP.

Given that SUDEP accounts for a high proportion of deaths in young adults with epilepsy (Sillanpää & Shinnar, 2010), the appropriateness of using the word “unexpected” might also be questioned. However, most persons with epilepsy do not die suddenly while otherwise healthy and engaged in normal activities. The word “unexpected” appropriately stresses the benign circumstances in which the death occurs suddenly.

WITH OR WITHOUT SEIZURE

An issue regarding the definition of SUDEP is whether cases with known terminal epileptic seizure occurrence should be separated from those without. Whereas the Nashef definition includes both types of cases, use of the Annegers definition varies in the literature. Some studies have separated those presumed to have occurred with a seizure from those without a seizure (Klenerman et al., 1993; Sillanpää & Shinnar, 2010). The distinction between cases with and without known terminal seizure would be useful in searching for potentially different underlying mechanisms, so that specific preventive strategies can be developed. However, it has been noted that such a distinction is not practical, particularly in epidemiologic studies, because most deaths are unwitnessed and information regarding a terminal seizure occurrence is often limited or unavailable (Nashef & Ryvlin, 2009). Except for studies of SUDEP events that had been recorded with video-electroencephalography (EEG) in an epilepsy monitoring unit, systematically collected data regarding terminal seizure occurrence are often circumstantial and limited, even in witnessed SUDEP cases. Insisting on a distinction between the two types of cases may constrain investigators to classify cases without reasonable certainty. Therefore, the category of SUDEP may be applied whether or not a terminal seizure is known to have occurred. The difficulty of classifying SUDEP cases according to terminal seizure occurrence should not prevent investigators from ascertaining and reporting completely all available evidence pertaining to a seizure occurrence close to the time of death. For studies that seek to distinguish

between SUDEP with and without terminal seizure, investigators should specify the criteria used for determining each type of SUDEP. An “Unknown” category should be used to include SUDEP cases in which evidence is insufficient to permit the distinction.

DISTINGUISHING CASES WITH INSUFFICIENT DATA AND CASES WITH COMPETING CAUSES

Another issue in classifying SUDEP arises when information on a death in someone with epilepsy is missing or when autopsy data are lacking, because autopsy was not performed or its data were unavailable or incomplete, which is often the situation in many countries (Coyle et al., 1994; de la Grandmaison, 2006). This issue is partly addressed in the Annegers definition, which classifies cases into “Definite,” “Probable,” “Possible,” and “Not SUDEP” cases. However, the Possible SUDEP category includes both cases with insufficient information and cases with competing causes of death. We agree with the late Dr. Annegers that it is important that these two types of Possible SUDEP cases be clearly distinguished from each other (Annegers, 1997). Therefore, we propose in the Unified SUDEP Definition and Classification that cases be left unclassified when data are insufficient to reasonably permit their classification, and that the Possible SUDEP category includes only cases with competing causes of death (Box 3).

Box 3. Proposed unified sudden unexpected death in epilepsy (SUDEP) definition and classification

1. *Definite SUDEP*:^a 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 (seizure duration ≥ 30 min or seizures without recovery in between), in which postmortem examination does not reveal a cause of death
- 1a. *Definite SUDEP Plus*:^a 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/Probable SUDEP Plus*:^a 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 A competing cause of death is present
4. *Near-SUDEP/Near-SUDEP Plus*: 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

^aIf a death is witnessed, an arbitrary cutoff of death within 1 h from acute collapse is suggested.

In some situations, evidence indicates that a preexisting condition could have contributed to the death, which otherwise is SUDEP. Examples are coronary insufficiency or long-QT syndrome in a case of sudden unexpected death associated with a habitual epileptic seizure, but autopsy fails to reveal myocardial infarction or other structural causes of death. We propose that such a situation be designated as “Definite SUDEP Plus,” since the preexisting conditions did not clearly cause sudden death, but they may have been essential contributors to the death (Nashef & Ryvlin, 2009). Without providing a category of Definite SUDEP Plus for such cases, they would likely be placed in the Possible SUDEP category; these cases as a rule are excluded from most research studies. Such exclusion would neglect the potential effects of coexisting disease. The prevalence of these preexisting conditions, whether known before or after autopsy, is currently unknown in persons with epilepsy and in persons who died of SUDEP. The creation of the Definite SUDEP Plus category provides the opportunity to investigate the role that these conditions have in causing SUDEP and whether treatment of the conditions could decrease the risk of these deaths. Definite SUDEP Plus does not require a seizure to have been witnessed or determined to have occurred close to the time of death. However, if the preexisting condition is shown to have caused death—for example, long-QT syndrome with documented primary ventricular arrhythmia leading to death—the case should be classified as Not SUDEP. On the other hand, if a seizure triggers a fatal arrhythmia in an individual with long-QT syndrome, the death would be classified as Definite SUDEP Plus.

SPECIFYING THE EXTENT OF AUTOPSY

It should be noted that negative findings on autopsy examination do not equate with a normal autopsy examination. Some degree of organ congestion, especially of the lungs, is commonly detectable at autopsy in cases of SUDEP, but not to a degree sufficient to cause acute death. Other findings may include evidence of a recent seizure, secondary anoxic changes, or underlying causes of the epilepsy. Autopsies vary considerably in their comprehensiveness and details in the historical information surrounding death, gross inspection of the body and organs, microscopic examination of tissues, and toxicologic and genetic studies. Requirements for an adequate or satisfactory autopsy examination are not specified in either the Annegers or the Nashef definition. The Nashef definition does state that autopsy examination should not reveal a toxicologic or anatomic cause of death. Nonetheless, the definition does not require toxicologic screening at autopsy, nor does it specify the extent of the anatomical examination. Given the ongoing advancements in screening capabilities and methods of toxicologic and genetic examinations, we are currently not proposing specific requirements in the extent of autopsy for defining and classifying SUDEP.

However, investigators should develop, specify, and update the autopsy protocols they use to optimize the extent of the autopsy examination.

TIME FROM TERMINAL EVENT

Time from terminal event to death is not specified in the Nashef definition but is indicated in the Annegers definition as within minutes (if known). It is difficult to apply such a categorical specification when most SUDEP cases are unwitnessed. Some definitions of sudden death in the general population refer to death occurring within minutes, or alternatively within 1 h, of the onset of acute symptoms. One study of SUDEP allowed for death to occur within hours of a terminal event (Leestma et al., 1997). Even assuming that most SUDEP cases are related to a terminal seizure, postictal mechanisms that potentially underlie SUDEP do not necessarily result in instantaneous death. Therefore, deaths that do not occur instantaneously during the postictal phase could still be classified as SUDEP. However, without some restriction in the time frame between the terminal event and death, other potential causes of death become more likely as the time frame becomes longer. When autopsy is not done, cases are classified as “Probable SUDEP,” but such classification becomes less plausible as the time frame increases. Therefore, we propose that, if the time of death from a terminal event is known, to be considered SUDEP, death should have occurred within 1 h from onset of the terminal event. Restricting the time frame to 1 h is more appropriate than “within minutes,” and less elusive than “within hours.” Admittedly, this time limit is arbitrary, but studies of witnessed SUDEP (Langan et al., 2000) and of cases that have occurred in epilepsy monitoring units suggest that cases occur within a shorter time frame and that 1 h is unlikely to exclude relevant cases of SUDEP (Ryvlin & Tomson, 2009; Bateman et al., 2010).

STATUS EPILEPTICUS

When known to have occurred, status epilepticus is a criterion that excludes SUDEP. However, it is acknowledged that in an unwitnessed death, it may not be possible to ascertain the occurrence of status epilepticus. Furthermore, there are different definitions of status epilepticus. For status epilepticus to be an exclusion criterion for SUDEP, we propose that the duration of seizure activity be 30 min or more.

ASPHYXIA OR SUFFOCATION AS A CONTRIBUTORY FACTOR

Asphyxia or suffocation has often been implicated as a cause of unexpected deaths in persons with epilepsy. Asphyxia or suffocation has been listed on death certificates in unexpected epilepsy deaths in the United States and the United Kingdom. Positional impediments to breathing due

to body position or obstructing materials such as bedding, or both, may be a contributory factor to SUDEP. This possibility is supported by the finding that persons with SUDEP have been found in a prone position significantly more often than would be expected by chance (Kloster & Engelskjøn, 1999). In another study of the circumstances surrounding 26 cases of SUDEP, 11 persons were found in a position that could have compromised breathing (Nashef et al., 1998). The role of suffocation from positional impediment to breathing in contributing to SUDEP should not be disregarded because it is potentially remediable. Repositioning, and perhaps stimulation, may well be the basis for the observation that supervision of epilepsy persons appears to be associated with lower SUDEP risk (Nashef et al., 1995). Nonetheless, ascribing SUDEP to asphyxia or suffocation alone may be simplistic, in view of the role of cerebral mechanisms demonstrated in several studies of periictal respiratory compromise (Nashef et al., 1996; Bateman et al., 2008; Tomson et al., 2008; Bateman et al., 2010). Furthermore, in cases with positional impediment to breathing, ictal and postictal coma likely contributes to death by preventing self-corrective action of reflexive repositioning, which fails to occur as PO_2 decreases and PCO_2 increases (Tao et al., 2010).

Furthermore, it may not be possible for autopsy examination to definitely establish the occurrence of asphyxia or to assess the relative contributions of different mechanisms (Nashef & Ryvlin, 2009). Therefore, we should not designate a specific category of SUDEP due to asphyxia. Nonetheless, the omission of the word “unexplained” in the term SUDEP would permit the diagnosis of SUDEP even when evidence of positional impediment to breathing is found. Such cases should be distinguished from rare non-SUDEP cases in which death was clearly due to asphyxia or suffocation alone, such as with strangulation (for examples, see Table 1).

DEATHS IN WATER WITHOUT EVIDENCE OF SUBMERSION

Deaths are classified as “Not SUDEP” if there is circumstantial or autopsy evidence of drowning. However, drowning can also occur without clear autopsy evidence (Lunetta et al., 2004). If the death occurs in water but without circumstantial or autopsy evidence of submersion, we recommend that the death be classified as Possible SUDEP.

NEAR-SUDEP

“Near-SUDEP” cases contribute to our understanding of SUDEP mechanisms. A unique setting in which Near-SUDEP is more commonly observed and recorded than in other settings is during video-EEG recording in epilepsy monitoring units. The definition used in an ongoing study of Near-SUDEP cases in epilepsy monitoring units is

Table 1. Case scenarios according to the proposed unified SUDEP definition and classification

Classification	Scenario	Comment
Definite SUDEP	Epilepsy patient, no other relevant preexisting conditions; found dead; negative postmortem examination ^a	Meets criteria for SUDEP
	Epilepsy patient; witnessed sudden death in sleep or during activity including exercise, no seizure; negative postmortem examination ^a	Meets criteria for SUDEP
	Epilepsy patient, no other relevant preexisting conditions; witnessed seizure, postictal coma, no evidence or history of terminal status epilepticus, dies within 20 min without regaining consciousness; negative postmortem examination ^a	Meets criteria for SUDEP
	Epilepsy patient found dead facedown in bed or in carpet pile; negative postmortem examination ^a	Fulfills criteria for Definite SUDEP. Although positional respiratory obstruction may be contributory, this is within the context of postictal coma, and position alone is not the cause of death
	Sudden death in conjunction with witnessed first seizure; postmortem examination shows meningioma without significant mass effect, otherwise negative	Has enduring predisposition for seizures and thus meets criteria for epilepsy
Definite SUDEP Plus	Epilepsy patient with known long-QT syndrome; witnessed sudden death without seizure; negative postmortem examination ^a	Meets criteria for Definite SUDEP, but with a concomitant condition that may have contributed to the death
	Epilepsy patient with known long-QT syndrome; found dead in bed; negative postmortem examination ^a	Witnessed seizure is not a requirement for either SUDEP or Definite SUDEP Plus
	Epilepsy patient; cardiorespiratory arrest after habitual seizure; postmortem examination shows coronary artery atheroma but no evidence of myocardial infarction	Postmortem evidence of a concomitant condition that may have contributed to the death
Probable SUDEP	Epilepsy patient, no other relevant preexisting conditions; found dead in bed in the morning, benign circumstances; no postmortem examination	Historical and circumstantial evidence strongly suggest SUDEP, but no postmortem examination was done to exclude another pathologic process
Possible SUDEP	Epilepsy patient, no other relevant preexisting conditions; found dead in water but not submersed, benign circumstances; no postmortem examination	Postmortem examination may have identified drowning. If present, this would exclude SUDEP
	Epilepsy patient, no other relevant preexisting conditions; found dead in water but not submersed, benign circumstances; postmortem examination does not show drowning	Drowning would have excluded SUDEP, but postmortem examination does not exclude dry drowning. There is a competing cause for death; thus, Possible SUDEP
	Otherwise healthy patient with uncontrolled epilepsy; found dead in the daytime; postmortem examination reveals aspiration of gastric contents of unspecified amount	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
Near-SUDEP	Epilepsy patient, no other relevant preexisting conditions; cardiorespiratory arrest after seizure, successfully resuscitated; evaluation shows no obvious cause of the cardiorespiratory arrest	
	Epilepsy patient; cardiorespiratory arrest after witnessed seizure, resuscitated but dies within a few days or weeks; negative postmortem examination ^a	Does not meet criteria for SUDEP because death occurred more than 1 h after initial cardiorespiratory arrest
Not SUDEP	Sudden death in conjunction with witnessed first seizure; negative postmortem examination ^a	Does not meet criteria for epilepsy, unless retrospective history shows indications of previous events suggestive of epilepsy
	Epilepsy patient, no other relevant preexisting conditions; witnessed seizure followed by severe aspiration of full stomach contents, resuscitation unsuccessful; postmortem examination shows severe aspiration	Postmortem examination finding of severe aspiration as cause of death excludes SUDEP. Minor aspiration may be observed in SUDEP
	Epilepsy patient; cardiorespiratory arrest after habitual seizure, resuscitated but dies after 5 days; postmortem examination shows large myocardial infarction	A clear cause of death is found by postmortem examination
	Epilepsy patient found dead in bed with neck stuck between bed railings; postmortem examination shows clear strangulation	The death does not fulfill criteria for SUDEP in that a clear cause of death was found at postmortem examination
	Epilepsy patient; found dead submersed in lake/pool where she swam	Immersion suggests drowning and excludes SUDEP

SUDEP, sudden unexpected death in epilepsy.

^aNegative postmortem examination for primary pathology causing death, despite the following potentially being present: underlying structural cause of epilepsy; organ congestion, particularly pulmonary; tongue bite; minimal aspiration; or petechial hemorrhages. There may also be evidence of resuscitation efforts or secondary anoxic injury.

cardiorespiratory arrest resolving after resuscitation procedure (Ryvlin P, oral communication, at the American Epilepsy Society meeting on December 3, 2010). For an event to be classified as Near-SUDEP, it must satisfy the other criteria for SUDEP, including the criterion that other causes of the cardiorespiratory arrest have been excluded. Although the term *Near-SUDEP* is more likely to be applied when a seizure is seen to have occurred immediately before the event, seizure occurrence need not be a requirement for the definition of Near-SUDEP.

In some instances, the resuscitation effort was initially successful, but death eventually occurred after a variable period of time because of anoxic brain injury or organ system failure. Such cases should still be classified as Near-SUDEP. Therefore, Near-SUDEP applies both to patients who survived after resuscitation and patients who were initially resuscitated but succumbed later to the complications of the initial cardiorespiratory arrest. Both cases are appropriately classified as Near-SUDEP because SUDEP could have ensued in either case if there was no resuscitative intervention. In other words, if the underlying pathophysiologic mechanisms were not interrupted, SUDEP would have occurred.

COMMENTS

SUDEP is particularly difficult to investigate in research studies because of its relatively low incidence, its unpredictable occurrence, especially in unwitnessed settings, and its low rate of complete autopsy examinations. We realize that any classification system is, to some extent, arbitrary and that other equally valid systems may be proposed. We have proposed here a definition and classification of SUDEP that would capture cases that otherwise might not have been considered for further investigation. The discovery of SUDEP mechanisms will not come solely from Definite SUDEP cases. Other SUDEP categories such as Definite SUDEP Plus, Near-SUDEP, and Possible SUDEP offer valuable opportunities to inform us about risk factors and mechanisms in SUDEP, which are likely to be heterogeneous. Investigators would be able to select from our proposed classification the SUDEP categories that are appropriate to the aims and requirements of each study. Moreover, we hope that investigators will accept this system as one that does not deviate substantially in concept and in application from what has been in use for many years.

Our proposed SUDEP definition and classification seeks to resolve ambiguities that exist with the prior Nashef and Annegers definitions and to retrieve cases that would not have been further studied if the prior definitions were used. Nonetheless, accurate fulfillment of criteria in any definition or classification system is critically dependent on the completeness of reliable data concerning the condition. An autopsy that has been declared negative for primary pathol-

ogy causing death and that supports a Definite SUDEP diagnosis may have been negative largely because the autopsy was very limited and because many important postmortem studies were not done. Therefore, the collection of information on every SUDEP case must be maximized to advance our understanding of why SUDEP happens and how it can be prevented. We agree with the recommendations of the American Epilepsy Society and Epilepsy Foundation Joint Task Force on SUDEP and the NINDS SUDEP Workshop that a standardized protocol for postmortem examination be developed and used (So et al., 2009; Hirsch et al., 2011), although full compliance with the protocol should not be a requirement for classification as Definite SUDEP. The optimal extent of premortem and postmortem data needed for SUDEP studies will continue to evolve as knowledge concerning epilepsy, seizures, or SUDEP itself is gained incrementally. For example, if in the future a reliable biomarker is found for recent seizure occurrence, it would be important to include a test for this in the postmortem examination protocol.

The diagnosis and classification of SUDEP will continue to be challenging for many cases, because the quality and amount of available data will vary from case to case. Our proposed classification involves precise application of certain principles and specific criteria in each SUDEP category. Table 1 describes scenarios that demonstrate the basis for each category. For cases in which disagreement exists, we suggest the use of consensus decision by a panel of informed reviewers to adjudicate the classification of the cases.

DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

- Annegers JF. (1997) United States perspective on definitions and classifications. *Epilepsia* 38(Suppl. 11):S9–S12.
- Bateman LM, Li CS, Seyal M. (2008) Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain* 131:3239–3245.
- Bateman LM, Spitz M, Seyal M. (2010) Ictal hypoventilation contributes to cardiac arrhythmia and SUDEP: report on two deaths in video-EEG-monitored patients. *Epilepsia* 51:916–920.
- Coyle HP, Baker-Brian N, Brown SW. (1994) Coroners' autopsy reporting of sudden unexplained death in epilepsy (SUDEP) in the UK. *Seizure* 3:247–254.
- de la Grandmaison GL. (2006) Is there progress in the autopsy diagnosis of sudden unexpected death in adults? *Forensic Sci Int* 156:138–144.
- Earnest MP, Thomas GE, Eden RA, Hossack KF. (1992) The sudden unexplained death syndrome in epilepsy: demographic, clinical, and post-mortem features. *Epilepsia* 33:310–316.
- Hirsch LJ, Donner EJ, So EL, Jacobs M, Nashef L, Noebels JL, Buchhalter JR. (2011) Abbreviated report of the NIH/NINDS workshop on sudden unexpected death in epilepsy. *Neurology* 76:1932–1938.
- Klenerman P, Sander JW, Shorvon SD. (1993) Mortality in patients with epilepsy: a study of patients in long term residential care. *J Neurol Neurosurg Psychiatry* 56:149–152.

- Kloster R, Engelskjøn T. (1999) Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. *J Neurol Neurosurg Psychiatry* 67:439–444.
- Langan Y, Nashef L, Sander JW. (2000) Sudden unexpected death in epilepsy: a series of witnessed deaths. *J Neurol Neurosurg Psychiatry* 68:211–213.
- Lathers CM, Schraeder PL. (1982) Autonomic dysfunction in epilepsy: characterization of autonomic cardiac neural discharge associated with pentylentetrazol-induced epileptogenic activity. *Epilepsia* 23:633–647.
- Leestma JE, Kalelkar MB, Teas SS, Jay GW, Hughes JR. (1984) Sudden unexpected death associated with seizures: analysis of 66 cases. *Epilepsia* 25:84–88.
- Leestma JE, Annegers JF, Brodie MJ, Brown S, Schraeder P, Siscovick D, Wannamaker BB, Tennis PS, Cierpial MA, Earl NL. (1997) Sudden unexplained death in epilepsy: observations from a large clinical development program. *Epilepsia* 38:47–55.
- Lunetta P, Modell JH, Sajantila A. (2004) What is the incidence and significance of “dry-lungs” in bodies found in water? *Am J Forensic Med Pathol* 25:291–301.
- Nashef L. (1997) Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia* 38(Suppl. 11):S6–S8.
- Nashef L, Ryvlin P. (2009) Sudden unexpected death in epilepsy (SUDEP): update and reflections. *Neurol Clin* 27:1063–1074.
- Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. (1995) Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia* 36:1187–1194.
- Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. (1996) Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *J Neurol Neurosurg Psychiatry* 60:297–300.
- Nashef L, Garner S, Sander JW, Fish DR, Shorvon SD. (1998) Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives. *J Neurol Neurosurg Psychiatry* 64:349–352.
- Ryvlin P, Tomson T; The MORTEMUS Study. (2009) MORTEMUS (Mortality in Epilepsy Monitoring Unit Study): preliminary findings [abstract]. *Epilepsia* 50(Suppl. 4):60.
- Sillanpää M, Shinnar S. (2010) Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 363:2522–2529.
- So EL. (2006) Demystifying sudden unexplained death in epilepsy: are we close? *Epilepsia* 47(Suppl. 1):87–92.
- So EL, Bainbridge J, Buchhalter JR, Donalhy J, Donner EJ, Finucane A, Graves NM, Hirsch LJ, Montouris GD, Temkin NR, Wiebe S, Sierzant TL. (2009) Report of the American Epilepsy Society and the Epilepsy Foundation joint task force on sudden unexplained death in epilepsy. *Epilepsia* 50:917–922.
- Tao JX, Qian S, Baldwin M, Chen XJ, Rose S, Ebersole SH, Ebersole JS. (2010) SUDEP, suspected positional airway obstruction, and hypoventilation in postictal coma. *Epilepsia* 51:2344–2347.
- Terrence CF Jr, Wisotzkey HM, Perper JA. (1975) Unexpected, unexplained death in epileptic patients. *Neurology* 25:594–598.
- Tomson T, Nashef L, Ryvlin P. (2008) Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol* 7:1021–1031.