SUDEP: Risk Factors and Proposed Mechanisms

Patients and families deserve information about their risk for SUDEP and steps that can be taken to minimize that risk.

By Michelle L. Dougherty, MD

Sudden Unexpected Death in an Epileptic Person (SUDEP) is a rare but real complication of epilepsy. Earlier this year the American Academy of Neurology (AAN) published guidelines detailing incidence rates and risk factors for SUDEP in both adult and pediatric populations.1 Given the low awareness amongst patients, physicians should discuss risk of SUDEP early in treatment and revisit the topic for higher risk patients.

Incidence
It has long been known that persons with epilepsy are at higher mortality risk than the general population. Patients with epilepsy have a two- to three-fold increase in mortality.2 Specific incidence of SUDEP, however, has been difficult to ascertain and varies based upon definition and population under study. A previous population estimate from Rochester, MN found a 23.7-fold increase in sudden unexpected death among patients with epilepsy when compared to the overall population, however, this risk is not evenly distributed.3

Studies of specific populations demonstrate significant variability in SUDEP risk; reported incidences range from 0.09 to 0.35 per 1,000 person years in community-based studies, and nine per 1,000 person years in candidates for epilepsy surgery.3,4 After review of 12 Class I studies providing incidence rate data with a random effects meta-analysis, authors of the 2017 AAN practice guidelines found a SUDEP risk of 0.22 per 1,000 patient years in children with epilepsy and 1.2 per 1,000 patient years in adults with epilepsy.1

Risk Factors
Risk factors for SUDEP previously identified include male sex, African American ethnicity, unwitnessed seizures, polytherapy, non-compliance with AEDs, symptomatic epilepsy, comorbid alcohol abuse, comorbid mental health disorders, treatment with SSRI antidepressants, longer duration of epilepsy, use of carbamazepine or lamotrigine, and uncontrolled seizures, especially greater frequency of generalized tonic-clonic seizures (GTCS).3,5 Many of these risks are related to or a marker of poorly controlled epilepsy. It therefore follows that, after systematic review of six Class I studies and 16 Class II studies, the 2017 AAN practice guidelines highlight presence and frequency of continued GTCS as the major risk factors for SUDEP.1 Specifically, patients with three or more GTCS per year are at 15-fold higher risk of SUDEP.1 Thus, continued attempts at improving seizure control are needed for patients who continue to experience SUDEP, as reduction in frequency of GTCS would be expected to have a beneficial effect on risk.

Also noted in the guidelines are protective effects. Specifically, the presence of another person in the same room who is older than 10 years of age and of normal intelligence, as well as use of a remote listening device, were found to be protective and reduce the risk of SUDEP.1 This protective effect suggests that assistance provided by someone in the room or able to check on the patient following an alert can help prevent SUDEP by mitigating the effect of postictal respiratory depression following a seizure. This nighttime surveillance may not always be easy to provide or allow for adequate privacy for the patient, but it may be beneficial in some settings if the patient and family are agreeable.
Proposed Mechanism

Most instances of SUDEP occur at night, as patient are often found in bed. They are also often found in a prone position or other position that could have contributed to respiratory compromise. Data to support proposed mechanisms come primarily from observed cases supplemented by post-mortem examinations and experimental animal models. Clinical data reveal that the majority of cases of SUDEP are triggered by a seizure.

Perhaps the most helpful reports of witnessed SUDEP come from the MORTEMUS study, which detailed events of SUDEP, near SUDEP, and other deaths in an epilepsy monitoring unit (EMU) setting. They found 16 SUDEP and nine near SUDEP cases, all of which were adults with nocturnal events occurring between 7:30pm and 6:00am (with the exception of one patient) that could be described as a cardiopulmonary arrest immediately following a seizure described as GTCS. Anti-epileptic drugs (AEDs) had been reduced or discontinued in a majority of cases, and the majority of cases in which the position could be documented the patient was found to be prone.

The recorded arrests had four consistent features following a GTCS:

1. Rapid breathing at rates of 18 to 50 breaths per minute immediately following seizure
2. Postictal generalized suppression of EEG
3. Cardiorespiratory dysfunction within three minutes after the seizure characterized by bradycardia and ultimately asystole
4. Terminal apnea followed by terminal asystole

The study authors suggested that SUDEP results from a postictal dysfunction of both respiratory and cardiac function, termed a “neurovegetative breakdown.” They also identified a potential window for intervention to prevent SUDEP in the three minutes following a GTCS. Post-mortem findings in patients who died due to SUDEP indicate neurogenic pulmonary edema, subendocardial myocardial vacuolization, and increased expression of heat shock protein 70 in hippocampal neurons. These pathologic findings may be consistent with cardiorespiratory failure seen in experimental models of SUDEP, such as the pulmonary edema and cardiac ischemia in sheep and rat models.

Recommendations for Discussion with Patients and Families

While there are still significant knowledge gaps surrounding SUDEP, most patients and families would like to know about the risk of SUDEP even if it is low, particularly if there are steps that can be taken to further minimize that risk. Clinicians should provide patients and families with information in clear, simplified terms in both a positive (e.g., risk of SUDEP) and negative (e.g., risk of not being affected by SUDEP) manner, so that patients will appropriately understand their risk.

The 2017 AAN practice parameter gives specific guidance for this discussion. Parents of children with epilepsy should be informed that SUDEP is rare, affecting one in 4,500 patients and conversely will not affect 4,499 of 4,500. Similarly, adults should be informed that they have a small risk of SUDEP, and in a single year SUDEP affects roughly one in 1,000 patients with epilepsy, meaning 999 in 1,000 will not be affected.

Finally, patients and families should be aware that seizure freedom is the most significant modifiable risk factor in preventing SUDEP. Ideally, a discussion of SUDEP risk and factors that influence risk could help patients and families take appropriate steps to lower that risk wherever possible, such as adherence to prescribed AEDs, continuing to pursue further treatments, and avoiding known seizure triggers.

SUDEP: Definite vs. Probable

The formal definition of SUDEP requires that the patient have a diagnosis of epilepsy, that deaths by drowning, trauma, and status epilepticus are excluded, and the absence of an alternate cause of death. Cases confirmed by autopsy are termed “definite SUDEP”; cases that are sudden and unexplained by other causes but do not have autopsy are termed “probable SUDEP.” “Possible SUDEP” can also be considered and is defined as a case of sudden unexplained death in a person with epilepsy with a possible alternate cause of death, though these cases are usually excluded from studies.

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