Sudden unexpected death in epilepsy

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A 57-year-old man with severe mental retardation and epilepsy was found unresponsive. The primary caretaker said that he was on the toilet, rolled his eyes, and stopped breathing. She did not witness either generalized tonic-clonic seizures or trauma. Cardiopulmonary resuscitation was initiated by family members; paramedics found him in asystole. The patient was intubated and flown to the nearest emergency department (ED). However, he remained in asystole and was pronounced dead.

The patient had tonic-clonic seizures every other month; his last one occurred approximately 2 weeks before his death. His antiepileptic drugs included valproic acid and phenytoin, and his primary caretaker administered all his medications. On physical examination in the ED, all vital signs were absent. General examination revealed a cyanotic and unresponsive man with absent corneal reflexes and dilated pupils. No laboratory tests were done in the ED. His last phenytoin and valproic acid levels were subtherapeutic 7 days prior to his death. His autopsy showed no fatal injuries or diseases. No intracranial hemorrhages or exudates were identified on gross examination, and microscopic findings did not identify any inflammatory infiltrates, hemorrhages, necrosis, or infarcts. Postmortem blood analysis revealed subtherapeutic phenytoin and valproic acid levels. Sterilely obtained blood cultures did not grow any pathogenic organisms, and vitreous electrolyte analysis showed no electrolyte abnormalities. The diagnosis of sudden unexpected death in epilepsy (SUDEP) was made based on the patient's clinical presentation and unremarkable autopsy.

DISCUSSION

SUDEP has been defined as “the sudden, unexpected witnessed or unwitnessed, non-traumatic, and non-drowning death of a subject with epilepsy with or without evidence for a seizure (excluding documented status epilepticus) in which the autopsy does not reveal a structural or toxicological cause of death” (taken from Nei and Hays¹).² The reported incidence of SUDEP depends on the cohort studied and ranges from 0.09 per 1,000 persons per year in population-based studies to 9.3 per 1,000 persons per year in intractable epilepsy surgery cohorts.² Overall, SUDEP causes 7%–17% of deaths in all patients with epilepsy and up to 50% of deaths in patients with refractory disease. Numerous risk factors have been associated with an increased risk of SUDEP; these include poor medication compliance, generalized tonic-clonic seizures, male sex, alcoholism, young adult age, and cognitive dysfunction. Polypharmacy, frequent changes in medication, and possibly some antiepileptic drugs, especially carbamazepine, also increase the risk for SUDEP.^{1,2}

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Figure Schematic overview of the pathogenesis of sudden unexpected death in epilepsy

SUDEP usually occurs in patients with generalized tonic-clonic or complex partial seizures; the pathophysiology of SUDEP is not well understood. Acute cardiac, respiratory, or cerebral dysfunction (“cerebral shutdown”) potentially explain SUDEP (figure).^{1–7} Ictal alterations in cerebral blood flow could precipitate this event by causing cerebral suppression that leads to central apnea, hypotonic respiratory muscles, or mechanical obstruction of the upper airway.^{1,2} Some patients with SUDEP may have alterations in the CNS serotonin system.⁶ These neurons originate in the midbrain, pons, and medulla, stimulate respiratory neurons in the medulla, and increase arousal through projections to the thalamus and cortical regions. Postictal dysfunction in these serotonin neurons could suppress essential respiratory and arousal responses after seizures and lead to acute respiratory failure. Extreme autonomic imbalance secondary to abnormal central nervous control of the parasympathetic system could also cause central apneas. Acute hemodynamic changes following adrenergic bursts increase the blood volume in the thorax, and sympathetic stimulation causes pulmonary venoconstriction resulting in neurogenic pulmonary edema.²

Catecholamine release caused by seizures reduces intraictal heart rate variability and increases postictal vascular tone, leading to persistent postictal tachycardia and QTc changes which increase the risk of fatal arrhythmias. QTc shortening, metabolic acidosis, and hyperkalemia reduce the ventricular refractory period and increase the risk for life-threatening re-entry ventricular tachyarrhythmias. Peri-ictal QTc prolongation secondary to vagal stimulation could also facilitate fatal ventricular tachyarrhythmia. Ictal apnea can provoke progressive bradycardia that is followed by asystole. Moreover, high local concentration of catecholamines and transient vasospasm can induce stress-induced cardiomyopathy leading to cardiogenic shock, heart failure, and sudden death.³

Cases of near-SUDEP have been reported in patients being studied with long-term video electroencephalography and telemetry. These cases provide critical information about acute events in SUDEP, and we have summarized the terminal events from representative publications in the table.^{3,7} These cases suggest that ictal and postictal stimulation of the autonomic nervous system and cerebral suppression cause autonomic instability and cardiorespiratory arrest. These patients usually have postictal flattening of the EEG.

Table Cases with near sudden unexpected death in epilepsy

Patient no. and reference	Sex	Age, years	Type of seizure	Recorded events
1 ⁶	F	20	Generalized tonic-clonic seizures	Seizure → central apnea → bradycardia → asystole → cardiopulmonary resuscitation
2 ³	F	27	Simple partial seizures, complex partial seizures	Seizure → AV block III → asystole → pacemaker implantation
3 ³	M	41	Simple partial seizures, complex partial seizures, secondary generalized tonic-clonic seizures	Seizure → sinus arrest → tachyarrhythmia/bradyarrhythmia → asystole → pacemaker implantation
4 ³	F	47	Simple partial seizures, complex partial seizures, secondary generalized tonic-clonic seizures	Seizure → AV block III → asystole → pacemaker implantation
5 ³	F	63	Simple partial seizures, complex partial seizures	Seizure → AV block III → asystole → pacemaker implantation
6 ³	M	65	Simple partial seizures, complex partial seizures, secondary generalized tonic-clonic seizures	Seizure → AV block III → pacemaker implantation
7 ³	F	55	Simple partial seizures, complex partial seizures, secondary generalized tonic-clonic seizures	Seizure → sinus arrest → tachyarrhythmia/bradyarrhythmia → asystole → pacemaker implantation
8 ³	F	23	Complex partial seizures, secondary generalized tonic-clonic seizures	Seizure → sinus arrest → tachyarrhythmia/bradyarrhythmia → asystole

In summary, SUDEP is strongly associated with active epilepsy, particularly in patients with generalized tonic-clonic seizures. The best approach to reducing SUDEP risk involves optimal seizure control. Patients, especially high-risk patients, and families need information about this diagnosis.

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DISCLOSURES

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/cp for full disclosures.