A 20-year-old man with intellectual disability and intractable multifocal epilepsy presented to a neurologist for further evaluation and management. His seizures began at 4 months, the night after his first DPT vaccine, and he continued to have frequent tonic-clonic seizures throughout his life. Several weeks after his visit, he was found facedown on the floor, dead, by his family. His autopsy was unremarkable, but genetic testing revealed a frame shift mutation in SCN1A, consistent with severe myoclonic epilepsy of infancy (Dravet syndrome).

Sudden unexpected death in epilepsy (SUDEP) remains a silent killer—often occurring in sleep when patients are alone and frequently eluding recognition by families, clinicians, coroners, and medical examiners. SUDEP is the death of a person with epilepsy that is not due to trauma, drowning, status epilepticus, suicide, or other known causes of epilepsy-related mortality. There is often evidence of an associated seizure, but the patient is usually found dead in the morning (1). In one 40-year cohort study of childhood-onset epilepsy, SUDEP caused 38% of all deaths (2). It is estimated that SUDEP kills more people (~3300/year) in the United States than fires (~3100) or sudden infant death syndrome (SIDS) (~2100) (3).

A variety of mechanisms likely cause SUDEP. Cases observed in the hospital and community have identified respiratory dysfunction, failure of protective reflexes, and cardiac arrhythmias (Figure 1 and ref. 1). Nearly all witnessed SUDEPs follow a terminal seizure, typically a generalized tonic-clonic seizure (GTCS). In case-control studies, the greatest risk factor for SUDEP was frequent GTCS (4). Aside from seizure control (5), little is known about how to prevent SUDEP.

Dravet syndrome (DS), or severe myoclonic epilepsy of infancy, is a rare genetic disorder usually due to mutations in the gene encoding a voltage-gated sodium channel, SCN1A. DS patients present in the first year of life with severe treatment-resistant epilepsy, intellectual disability, and gait disorder, and have a greater risk of premature death. Among DS children, the estimated risk of SUDEP is 6% per decade (6). In contrast, in community cohorts of children with epilepsy, SUDEP occurs in approximately 0.2% per decade (1). This 30-fold increase is a call to action to find the cause(s) of SUDEP in DS, identify high-risk patients, and translate mechanism into preventive strategies.

Kalume and colleagues’ characterization of SUDEP in a mouse model is an enormous step forward, uncovering mechanisms and suggesting preventive therapy (7). Similar to SUDEP in patients without DS, these mice died after GTCS, especially when there were multiple seizures. However, unlike human SUDEPs captured on video-EEG, where postictal respiratory dysfunction and electrocerebral suppression are the most common apparent culprit(s) (1), the DS mouse SUDEPs appeared to result primarily from asystole due to seizure-related parasympathetic hyperactivity. Treatment with a muscarinic receptor competitive antagonist reduced the incidence of SUDEP in DS mice. These investigators further refined the mechanism with selective knockouts, demonstrating that brain, rather than cardiac SCN1A, mediates SUDEP. These results point to defective neurocardiac coupling. It is still unclear whether the ictal parasympathetic hyperactivity in the Scn1a-mutant mice was a direct result of GABAergic neuronal Na+ current loss, the consequence of adaptive responses, or caused by changes in autonomic centers resulting from frequent, recurrent seizures.

Basic science rarely provides clinicians with such a clear target, yet the gap between mice and humans and between benches and bedside remains great. Why do these mice suffer SUDEP in a relatively restricted period of youth, unlike humans with DS, for whom the risk of SUDEP persists? Is ictal parasympathetic hyperactivity and bradycardia a major cause of SUDEP in human DS? Ictal asystole and significant bradycardia occur in approximately 1% of epilepsy patients, but in a small series of patients who were implanted with pacemakers for ictal asystole, no devices were activated over a mean 3-year follow-up period (8). Thus, ictal asystole appears to be benign in adults with epilepsy. Furthermore, refractory epilepsy patients show excessive sympathetic activation between, during, and after seizures (9). If the DS mouse findings are confirmed in human DS, the generalizability to all SUDEP is unclear.

Sadly, the mechanism of death in human SUDEP—DS or otherwise—remains poorly understood. Do nonfatal seizures in DS provide phenocopies of physiological changes in fatal seizures? We don’t know. Without biomarkers for SUDEP in DS patients, it would be premature to extend these murine findings to humans. In the meantime, we should focus resources on education and therapies to reduce GTCS frequency and other SUDEP risk factors.

The limitation of this study is what was not studied. Despite elegant experiments suggesting that cardiac parasympathetic hyperactivity is part of the terminal cascade, doubt remains whether it is sufficient to cause SUDEP in DS. Could a sympathetic rebound cause the terminal changes as suggested by some of the authors’ data (Figure 4A; ref. 7)? What about the brain and the lungs? Could seizure-induced brain changes outside of the medullary cardio-regulatory nuclei contribute to SUDEP in these mice? Kalume and colleagues’ mice had postictal EEG suppression, but they do not discuss its potential role. What roles do central and peripheral respiratory function play? And what of serotonergic, adrenergic, and purinergic neurotransmitters that have been implicated in other models of SUDEP (10)? Future animal studies should record multiple physiological parameters, including serum O2 and CO2 levels, respiratory rate, and cardiac and pulmonary histology. Perhaps the most important question raised by this study for clinicians caring for patients...
with epilepsy is whether or not the lessons of SUDEP in DS inform our understanding and prevention of SUDEP in the more than 99% of epilepsy patients without DS.

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