

This rare disorder is a call to arms for doctors and patients to control seizures.

BY ANDREW WILNER, M.D.

ohn Travolta's 16-year-old son, Jett, who suffered from uncontrolled seizures, died suddenly on Jan. 2, 2009, while on vacation with his family in the Bahamas. After an autopsy, "seizure" was listed as the cause of death. Later that year, in another heart-wrenching case, Steve Wulchin went to wake his 19-year-old son, Eric, and found him lying on the floor of their home in Boulder, CO. Eric, whose last seizure was six months before, had died unexpectedly during the night.

These two high-profile cases have heightened public awareness of sudden unexplained death in epilepsy (SUDEP), a rare disorder responsible for 2 percent to 18 percent of deaths in people with epilepsy. Recently, discussions about SUDEP have increased between physicians, patients, and their families. Currently, the most effective way to prevent SUDEP appears to be seizure control. However, even with the best care, sometimes SUDEP still occurs, and

researchers are looking for new ways to prevent it.

There are several known causes of death due to seizures: Status epilepticus (seizures lasting longer than 30 minutes or repeated seizures without recovery); accidental death such as head injury and drowning; suicide; and deaths from medical illness such as heart or lung failure made worse by a seizure. Many of these deaths may be prevented by good medical and mental health care, strict adherence to medications, and restrictions on dangerous activity such as driving, operating dangerous machinery, or swimming alone.

The American Epilepsy Society defines SUDEP as a "Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus where postmortem examination does not reveal

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a cause for death." Cases that fulfill most of these criteria may be designated "probable" or "possible" SUDEP.

#### **UNRAVELING THE MYSTERY**

Sudden unexpected death in epilepsy occurs in approximately 1 out of 1,000 people with epilepsy each year. Because it is so rare, it is difficult to study. Epileptologists who care for thousands of people with epilepsy will see only a handful of cases during their entire careers. Most deaths due to SUDEP, like Jett Travolta's and Eric Wulchin's, are unwitnessed, increasing the mystery.

Shlomo Shinnar, M.D., Ph.D., professor of neurology, pediatrics, and epidemiology and population health, and Director of the Comprehensive Epilepsy Management Center at Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY, explains that while one can make a probable SUDEP diagnosis clinically, an autopsy is necessary to make a definitive diagnosis because other causes must be ruled out.

"For example, SUDEP would not be considered a cause of death in someone who had a known brain tumor," Dr. Shinnar says.

Many experts believe that SUDEP is caused by cardiac or respiratory arrest related to abnormal electrical activity in the brain. Progress in research studies has begun to shed light on possible causes underlying this devastating disorder, which may lead to effective prevention strategies.

People with uncontrolled or refractory epilepsy are at highest risk of SUDEP, according to Jacqueline French, M.D., professor of neurology at New York University School of Medicine, New York, NY. (See box, "Probable Risk Factors for SUDEP.") In this group, SUDEP may occur in 1 out of 150 patients each year. "Taking medication regularly to avoid seizures is an important precaution that a person with epilepsy can take to avoid SUDEP," Dr. French says, adding that the risk of SUDEP also decreases with successful epilepsy surgery.

Cynthia Harden, M.D., professor of neurology and Director of the Epilepsy Division at North Shore-Long Island, agrees about the importance of seizure control. "Some risk factors for SUDEP are modifiable by achieving better seizure control, especially control of nocturnal seizures, with the goal of seizure freedom," she says.

"Recognizing risk factors and intervening to reduce the risk of SUDEP is an ongoing endeavor," Dr. Harden says. "I think there has been significant progress in understanding of the most important risk factors—and possibly even in terms of prevention, in that positioning of the patient during sleep may be important, as it is in Sudden Infant Death Syndrome [SIDS]. There is also research that suggests that a seizure may cause overstimulation of the heart, leading to an irregular heart beat and death, although how to prevent this cascade of events is not yet known."

Dr. Harden recommends that patients sleep on their sides or backs, not on their stomachs. (In their "Back to Sleep" campaign, the American Academy of Pediatrics recommends that children sleep on their backs to prevent SIDS.) Dr. Harden's

recommendation is based on research revealing that many SUDEP victims die in the prone position.

### Probable Risk Factors for SUDEP

- 1. Poor seizure control
- 2. Tonic clonic seizures
- 3. At least several years of epilepsy
- 4. Seizures at night
- 5. Young age (approximately 20 to 40 years of age)
- 6. Male
- 7. Mental retardation
- 8. Multiple antiepileptic drugs at the same time
- **9.** Poor medication adherence with low drug levels
- Genetic predisposition: This may play a role, but it is under investigation.

Sources: So et al. *Epilepsia* 2009; Nouri and Balish **eMedicine.Medscape.com** 2009; Goldman et al. *Science Translational Medicine* 2009.

### **POSSIBLE GENETIC FACTORS**

Jeffrey Noebels, M.D., Ph.D., professor of neurology, neuroscience, and molecular and human genetics at Baylor College of Medicine, Houston, TX, and colleagues have identified a genetic mutation in mice responsible for abnormalities in both heart and brain rhythms known as "Long QT syndrome" (also known as "Prolonged QT syndrome"). This gene may be responsible for cases of sudden cardiac death and SUDEP in mice. If the mouse model is correct. a similar genetic mutation in humans may put people at risk for SUDEP. Further studies are ongoing, including diagnostic strategies to improve risk prediction and prevention in people at risk of sudden death due to heart or brain arrhythmias.

"The genetic mutation identified by Dr. Noebels could play a role in many instances of SUDEP," Dr. Harden says. "The exciting part is that if this research pans out to the clinical

## Sleeping on your back instead of your stomach may help to prevent SUDEP.



OUT OF THE BLUE Eric Wulchin had not had a seizure in six months.

arena, the gene variation could be screened for in patients with epilepsy and lead to a clear intervention. I interview patients and families very carefully for signs and symptoms of Prolonged QT syndrome, and I often order an EKG to evaluate the heart rate and rhythm, which I review myself. If I find abnormalities, I refer the patient to a cardiologist."

### A FRANK DISCUSSION

Should a person with epilepsy ask her neurologist about SUDEP? She might get different responses, depending on the neurologist's perspective. Whether to discuss SUDEP and in how much detail remains a topic of hot debate among people with epilepsy and epileptologists. Some neurologists, such as Michael Sperling, M.D., Baldwin Keyes Professor of Neurology and director of the Jefferson Comprehensive Epilepsy Center at Thomas Jefferson University Hospital, Philadelphia, PA, believe that discussing SUDEP with people with controlled epilepsy has no benefit, because the person's risk of SUDEP is so low.

Others, such as Dr. French, feel differently. Dr. French has discussed SUDEP with many of her patients. However, Dr. French doesn't raise the possibility of SUDEP at a patient's first visit because there is so much information about epilepsy to convey. Instead, she waits until her patients are more comfortable with the diagnosis and treatment of epilepsy.

Some family members feel betrayed when someone dies of SUDEP if they were never told about this possibility. Although learning about SUDEP may be frightening, this knowledge may serve as an incentive for people with uncontrolled seizures to work more closely with their physicians, take their medications as directed, and consider epilepsy surgery and other treatments in order to control their seizures.

In 2009, the American Epilepsy Society and the Epilepsy Foundation Joint Task Force on SUDEP recommended that information about SUDEP should be provided to people with epilepsy, their families, and caregivers in the context of general epilepsy education and according to the person's risks. (See box, "Probable Risk Factors for SUDEP.") For example, people with absence seizures (petit mal) have relatively low risk, while those with convulsive seizures are at higher risk. The task force recommended that a clear presentation of the risks of SUDEP is a priority for patients who don't take their medication as directed and for whom epilepsy surgery represents a chance for seizure control.

For Dr. Shinnar, the age of his patient influences his decision about whether to discuss SUDEP. "I discuss SUDEP with my adult patients with uncontrolled seizures," he says, "but not usually at the first meeting. In children, I generally do not, as the risk of SUDEP in otherwise normal children does not ap-

pear to be higher than the risk of unexplained death in children without epilepsy. The risk does not rise until adolescence."

#### WHAT YOU CAN DO TO PREVENT SUDEP

According to the Report of the American Epilepsy Society and the Epilepsy Foundation Joint Task Force, the best strategy to prevent SUDEP appears to be effective seizure control, especially of generalized convulsive seizures. For people with epilepsy, this advice translates into taking antiepileptic medications as directed, keeping a record of seizure activity, maintaining a healthy lifestyle that avoids excessive alcohol, illicit drugs, and sleep deprivation, and working closely with a doctor and health care team. (For more on keeping a record of seizure activity, read "Dear Seizure Diary" on the Neurology Now Web site at bit.ly/epilepsydiary)

Steered by the knowledge that patients with uncontrolled seizures are at highest risk of SUDEP, Dr. French is studying the frequency of death in a six-year study of her patients with uncontrolled (refractory) epilepsy. In addition, Drs. French and Harden are working with colleagues at the American Academy of Neurology to write an evidence-based guideline on SUDEP, which will be available to all physicians and assist them in counseling their patients. A SUDEP registry has also been established for children at the University of Toronto in Canada.

Many educational resources are available for people with epilepsy, their families, and caregivers, to learn about SUDEP. (See Resource Central, page 35.) Steve Wulchin is now leading the Epilepsy Therapy Project's SUDEP Task Force. With increased education and research, tragic deaths like Jett's and Eric's should become far less frequent.



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- ► eMedicine Medscape, "Sudden Unexpected Death in Epilepsy": bit.ly/1UowAG
- ► Huffington Post, "Jett Travolta dies, son of John Travolta, Kelly Preston": huff.to/981uUh
- Neurology Today, "A Teenager's Death Turns Spotlight On Sudden Unexplained Death in Epilepsy": bit.ly/cqUqUa
- Neurology Today, "Cardiac Role in Sudden Unexplained Death in Idiopathic Epilepsy is Observed in Animal Models": bit.ly/9p1ZnP
- ► New York Times, "Unmasking Silent Killer in Epilepsy": nyti.ms/c5sOul



For more information on sudden unexpected death in elilepsy, see RESOURCE CENTRAL on page 35.