(Austin Publishing Group

Editorial

Sudden Unexpected Death in Epilepsy

Sanjeev V. Kothare^{1*}and Joseph Kaleyias²

¹Department of Neurology, New York University Langone Medical Center, USA ²Department of Paediatrics, Southend University Hospital, Essex, UK

*Corresponding author: Sanjeev V. Kothare, Department of Neurology, Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, NY, USA, Tel: +646 558 0806; Fax: +646 385 71643; Email: Sanjeev.Kothare@nyumc.org

Received: January 13, 2015; Accepted: January 27, 2015; Published: February 12, 2015

Sudden unexpected death in epilepsy (SUDEP) is defined as a "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning 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 for death" [1]. SUDEP cases are classified as: (1) definite when clinical criteria are met and autopsy reveals no alternative cause of death (2) probable when clinical criteria are met but there is no postmortem examination, and (3) possible when there is an alternative cause of death or when clinical data are lacking [1,2]. It has now become clear that SUDEP is associated with seizures though unwitnessed [3].

SUDEP is one of the leading causes of death in young and otherwise healthy adults with epilepsy and it is the most common cause of death that can be directly attributable to epilepsy [4,5]. More than 20% of patients with childhood-onset epilepsy who fail to achieve long-term seizure freedom will die of SUDEP within 40 years of follow-up [6]. The incidence per 1000 patient-years varies with the sample population, increasing from 0.09 to 2.65 in community samples to 1.2 to 5.9 in tertiary care epilepsy centers to 6.0 to 9.3 among patients evaluated for or treated with epilepsy surgery or vagus-nerve stimulation for epilepsy [3].

The underlying mechanism of SUDEP remains unclear. Sudden, unexpected death in epilepsy usually occurs in chronic, refractory cases of epilepsy, often in patients with a history of neurologic insult. However, sudden death can occur early in the course of epilepsy and in patients who have seizures only rarely [3]. Determining the precise mechanism of death is difficult, even in cases that were recorded on video EEG during the terminal event [3,6]. There is not a single mechanism to explain the mechanisms of SUDEP. Potential mechanisms may include: 1) cardiac arrhythmias (possibly related to the spread of seizures to the cardiovascular centers in the insular cortex), 2) ventilatory impairment with hypoventilation, prolonged apneas, or oxygen desaturations triggered by seizures, 3) impaired righting responses leading to suffocation (most patients with SUDEP have been found to be in the prone position), 4) autonomic instability during or after a seizure, and/or 5) postictal serotonin (5-HT) neuronal dysfunction causing depression of breathing, impaired arousal, and repositioning reflexes [6].

Knowledge of SUDEP risk factors has recently advanced thanks to the pooled analysis of four major case–control studies performed by the Subcommission on Mortality of the ILAE Commission on Epidemiology [8,9]. The main risk factor was found to be the presence and frequency of generalized tonic–clonics seizures (OR>15 for patients with \geq 3 GTCS/ month) [9]. Other SUDEP risk factors are the gender (male), the age of onset of epilepsy (< 16 years of age), the duration of epilepsy (>15 years), use of polytherapy (OR<2), underlying neurological deficits, nocturnal seizures [8].

A high seizure frequency remains the biggest conclusively substantiated underlying risk factor [7]. The severity of epilepsy partly explains some of the risk factors for sudden death, such as tonic- clonic seizures, frequent seizures, early onset and long duration of epilepsy, and polytherapy, but some factors probably contribute to the risk of sudden death directly [3]. The association of early onset and long duration of epilepsy with an increased risk of sudden death suggests that progressive neural changes contribute to the risk [3]. Although polytherapy is a marker of treatment-resistant epilepsy, treatment with three or more antiepileptic drugs has been found to increase the risk of sudden death by a factor of more than 8 after adjustment for seizure frequency [10]. However, in randomized, controlled trials involving patients with treatment-resistant epilepsy, the rate of sudden death was increased by a factor of more than 7 among patients who received placebo as compared with those who received an additional antiepileptic drug [11]. Diurnal seizure variability provides the opportunity to select appropriate timing with higher dosing in an attempt to achieve higher AED levels around the time when seizures occur most frequently [12]. Noncompliance and use of recreation drugs and alcohol abuse are other contributory factors.

A significant proportion of patients with epilepsy experience cardiac and respiratory complications during seizures. These cardiorespiratory complications are suspected to be a significant risk factor for SUDEP [7].

Several cardiac changes occur during seizures as a result of ictal autonomic dysfunction. Sympathetic responses (causing tachycardia and hypertension) are more common as compared to parasympathetic responses (causing bradycardia and hypotension). Combinations of sympathetic and parasympathetic activation and inhibition may occur simultaneously or sequentially during individual seizures [7]. Other cardiac abnormalities that may occur include asystole, repolarization anomalies (prolonged or shortened QTc interval), and atrial fibrillation. These possibly may arise from seizures arising from the insular cortex. Electrocardiography (EKG) indicators of abnormal cardiac repolarization during seizures (such as prolonged or shortened QTc interval) are risk factors for life threatening tachyarrhythmia and sudden cardiac death. A few studies have shown that mutations in certain genes could lead to predisposition to cardiopulmonary complications during seizures [13,14]. Investigation of key ion channel genes should be pursued

Sanjeev V. Kothare

to investigation the relationship between epilepsy and sudden death [15].

Seizure-induced respiratory changes can be lethal and may involve pulmonary dysfunction and suppression of brainstem respiratory and arousal centers [16]. These changes have been repeatedly demonstrated in numerous studies and include central and obstructive apneas, hypoventilation, hypercapnia, and desaturation with metabolic acidosis, bradypnea, and tachypnea. The most serious of these changes are those associated with respiratory depression (such as hypoxemias and central apneas) most commonly observed in young men with symptomatic generalized, contralaterally spreading, left or right temporal, longer-duration seizures [7]. Serotonin, a neurotransmitter, has beenshown to affect brainstem respiratory center excitability. Changes in serotonin levels have been reported in patients with sudden infant death syndrome (SIDS), and may also be contributing to the terminal events with SUDEP [17].

Cerebral shutdown is a yet another putative mechanism causing SUDEP that has been proposed. Postictal generalized electroencephalography suppression (PGES) which is a hallmark of cerebral shutdown, is defined as the immediate postictal (within 30 s), generalized absence of electroencephalographic activity >10 μ V in amplitude, allowing for muscle, movement, breathing, and electrode artifacts [18]. Prolonged PGES (>50 s) may be an independent risk marker for SUDEP [7]. It is however not clear whether PGES is an indirect or direct marker of cerebral dysregulation.

The effects of prolonged postictal EEG suppression, apnea, pulmonary shunting and edema, suffocation in the prone position, impaired arousal to hypercapnia, laryngeal spasm, and respiratory acidosis probably combine and cascade with cardiac factors to cause many cases of sudden, unexpected death in patients with epilepsy [3].

Can SUDEP be prevented? No prospective or controlled studies have evaluated interventions to reduce its incidence. Since a tonicclonic seizure precedes most sudden deaths in patients with epilepsy, seizure control and the appropriate use of medication as well as counseling on lifestyle is the focus of prevention [3]. Prevention might in turn target a number of contributing factors, with the aims of: (1) reducing the occurrence of GTCS with optimal treatment, (2) detecting postictal cardiorespiratory distress (seizure, SpO2, ECG monitor), (3) reducing the risk of upper airways partial obstruction and postictal respiratory distress (latticepillow, supervision, O2), (4) reducing central hypoventilation through physical stimulation, (5) reducing endogenous opioid and/or adenosine mediated postictal brain and brainstem depression, and (6) reinforcing serotonin related respiratory rescue mechanisms (SSRI) [3].

A discussion of sudden, unexpected death in epilepsy may be worthwhile for patients with tonic–clonic seizures who are beginning an antiepileptic-drug regimen and for patients at high risk for recurrent tonic–clonic seizures who are discontinuing such a regimen [3]. The 2007 UK National Institute for Health and Clinical Excellence (NICE) guidelines for epilepsy recommend disclosing the risk of sudden unexpected death in epilepsy SUDEP) to patients. The majority of parents wanted to know about SUDEP and its associated risks. Whenever possible, SUDEP information should be given by the physician accompanied by an information leaflet [19]. The identification of populations at high risk of SUDEP is of paramount importance in order to be able to test the impact of potentially preventive interventions so as to achieve a reduction of SUDEP.

References

- 1. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia. 1997; 38: S6-8.
- 2. Annegers JF. United States perspective on definitions and classifications. Epilepsia. 1997; 38: S9-12.
- Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med. 2011; 365: 1801-1811.
- Nilsson L, Ahlbom A, Farahmand BY, Tomson T. Mortality in a populationbased cohort of epilepsy surgery patients. Epilepsia. 2003; 44: 575-581.
- Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia. 2012; 53: 227-233.
- Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. N Engl J Med. 2010; 363: 2522-2529.
- Kothare SV, Singh K. Cardiorespiratory abnormalities during epileptic seizures. Sleep Med. 2014; 15: 1433-1439.
- Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y. Combined analysis of risk factors for SUDEP. Epilepsia. 2011; 52: 1150-1159.
- Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia. 2012; 53: 249-252.
- Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet. 1999; 353: 888-893.
- Nei M, Ho RT, Abou-Khalil BW, Drislane FW, Liporace J, Romeo A, et al. EEG and ECG in sudden unexplained death in epilepsy. Epilepsia. 2004; 45: 338-345.
- Guilhoto LM, Loddenkemper T, Vendrame M, Bergin A, Bourgeois BF, Kothare SV. Higher evening antiepileptic drug dose for nocturnal and earlymorning seizures. Epilepsy Behav. 2011; 20: 334-337.
- Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noebels JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med. 2009; 1: 2ra6.
- Glasscock E, Yoo JW, Chen TT, Klassen TL, Noebels JL. Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. J Neurosci. 2010; 30: 5167–5175.
- Tu E, Bagnall RD, Duflou J, Semsarian C. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. Brain Pathol. 2011; 21: 201-208.
- 16. Richerson GB, Buchanan GF. The serotonin axis: Shared mechanisms in seizures, depression, and SUDEP. Epilepsia. 2011; 52 Suppl 1: 28-38.
- Duncan JR, Paterson DS, Hoffman JM, Mokler DJ, Borenstein NS, Belliveau RA, et al. Brainstem serotonergic deficiency in sudden infant death syndrome. JAMA. 2010; 303: 430-437.
- Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol. 2010; 68: 787-796.
- Gayatri NA, Morrall MC, Jain V, Kashyape P, Pysden K, Ferrie C. Parental and physician beliefs regarding the provision and content of written sudden unexpected death in epilepsy (SUDEP) information. Epilepsia. 2010; 51: 777-782.