Update on Sudden Unexpected Death in Epilepsy

Essay

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By

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List of Abbreviations

Abbreviation	Meaning
AD	Autosomal dominant inheritance
AEDs	Antiepileptic drugs
ANS	Autonomic nervous system
AR	Autosomal recessive inheritance
AVN	Atrioventricular node
Brs	Brugada syndrome
CASQ2	Calsequestrin 2 gene
CI	Confidence interval
CMZ	Carbamazepine
COX	Cycoloxygenase
CPS	Complex partial seizures
CPVT	Catecholaminergic Polymorphic Ventricular tachycardia
CSD	Cortical spreading depression
CVS	Cardiovascular system
CVA	Cerebrovascular accidents
dACC	Dorsal Anterior Cingulate Cortex
ECG	Electrocardiogram
EEG	Electroencephalogram
EFNS	European federation of neurological societies
EtoH	Ethanol related
FEV	Functional Expiratory Volume
fMRI	Functional Magnetic Resonance Imaging
FVC	Forced Vital Capacity
GTC	Generalized tonic clonic
HRQOL	Health related quality of life
HRV	Heart rate variability
IA	Ictal asystole
IGE	Idiopathic generalized epilepsy
LAED	Low Antiepileptic drugs

LEV	Levetiracetam
LGS	Lenox Gestaut syndrome
LQTS	Long QT syndrome
LTG	Lamotrigine
MI	Motivational interviewing
NREM	Nonrapid eye movement
OSAS	Obstructive sleep apnea syndrome
PGES	Postictal generalized EEG suppression
PUFAs	Polyunsaturated fatty acids
PWE	People with Epilepsy
QTc	Corrected QT interval
RCT	Randomized clinical trial
REM	Rapid eye movement
RRP	Relative refractory period
RTAs	Road traffic accidents
Ryr	Ryanodine receptor
SCD	Sudden cardiac death
SE	Status Epilepticus
SMR	Standardized mortality ratio
SQTS	Short QT syndrome
SUDEP	Sudden Unexpected death in Epilepsy
SV2A	Synaptic vesicle 2A
Tdp	Torsade de pointes
Tks	Takotutsubo syndrome
TLE	Temporal lobe epilepsy
vACC	Ventral Anterior cingulated cortex
VET	Video EEG telemetry
WHO	World health organization

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Introduction

Epilepsy is a major cause of morbidity and mortality. It is reported to cause 2-3 times increased mortality rate than in those of general population, with most deaths in first 10 yrs after diagnosis **(Aboukhalil et al., 2012)**. Epilepsy is ranked as the fifth highest cause of lost years of life before age 75 for males and eighth highest for females. A cohort study of people with epilepsy dying over an 8 year period showed 30 % died of accidents (mostly drowning and burns) , 23% died suddenly, 16% status epilepticus and 14 % committed suicide **(Ridsale et al., 2011).**

It has long been recognized that otherwise well individuals with epilepsy can die suddenly. Suffocation or asphyxia during a convulsion was considered a likely mechanism by Delasiauve. His description focused on extrinsic mechanisms **(Delasiauve, 1854 quoted by Engel and Pedley, 2007)**. Early in the 20^{th} century based on experience at Craig colony, Spratling described epilepsy as a disease that destroys life suddenly and without warning through a single brief attack unaided by an accident to the patient at the moment, such as suffocation or fracture of the skull from falling, and does so in 3-4% of those who suffer from epilepsy **(Spratling, 1904 quoted by Engel and Pedley, 2007).** In the same time period,

Munson reported on mortality from Craig Colony in New York which housed patients with intractable epilepsy and found that 99 out of 582 deaths were sudden **(Munson, 1910 quoted by Lhatoo et al., 1999)**. It is now well recognized after a period of intense debate and challenge that sudden death is a genuine danger and cause of threat to epileptic patients **(Nashef and Tomson, 2008).**

Sudden Unexpected Death in Epilepsy (SUDEP) has been defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence that seizure has occurred, excluding documented Status Epilepticus **(Nashef and Brown, 1996).** The term "Definite SUDEP" requires postmortem analysis showing no definite cause of death (such as illicit drugs or acute myocardial infarction (MI) while the term "Probable SUDEP " is used when postmortem examination is not performed but definition is otherwise fulfilled. Meanwhile the term "Possible SUDEP" is applied to less clear cases that might have been SUDEP but where there is inadequate information to be certain or competing possible causes of death **(Hirsh et al., 2011).**

In population based studies SUDEP incidence rate is reported to be between 1:500 and 1:1000\yr **(Opeskin and Berkovic, 2003).** However it is reported to occur in persons

with uncontrolled seizures at a rate of 1 in 150 persons-years **(Tomson et al., 2005)**. It is the commonest cause of Epilepsy related deaths in patients with refractory epilepsy **(Vegni et al., 2011)**,

Unfortunately to date, the exact mechanisms and ways of preventing SUDEP are largely unknown. Theories on SUDEP have mainly concentrated on cardiac arrhythmias or pulmonary dysfunction as the main cause of death **(Hirsh, 2011).**

Most studies suggest that SUDEP occurs more commonly in those with frequent seizures. **(Opeskin and Berkovic, 2003).**

The main issue that needs to be thoroughly discussed is whether a program for prevention of SUDEP can be developed. A program similar to that done for prevention of Sudden infant death syndrome may substantially reduce its incidence. SUDEP prevention could start with identification of most prominent risk factors and terminal events associated with SUDEP **(So, 2006).**

This review is intended to identify an update on SUDEP, assess progression in understanding of SUDEP and suggest possible ways of its prevention as well as what message to be conveyed to epileptic patients and at what point should the risk of SUDEP be discussed with epileptic patients and their families.

Aim of the Work

To review the available evidence on possible mechanisms and risk factors for SUDEP and to suggest possible programs for prevention.

Overview on Mortality in Epilepsy

Epilepsy is a significant cause of mortality, despite that the risk factors for death in epilepsy are not well understood.

Mortality from all medical causes in the general population in England and Wales declined by 16% between 1993 and 2005. In contrast, mortality from epilepsy in that time period increased by 31% in males and 39% in females **(Ridsale, et al., 2011).** Estimates of death in epilepsy were described in a retrospective cohort study on deaths in epileptic patients over an 8 year period and showed that the causes were: Sudden unexpected death in epilepsy (SUDEP) (23.3%), accidents including drowning (30%), status epilepticus (16%) and suicide (14%) **(Fukuchi et al., 2002).**

SUDEP:

Will be thoroughly discussed later. A brief outlook is given here about other causes.

Accidents:

People with epilepsy are at increased risk for accidents which at times may be serious and even fatal. The risk of

accidents is partly due to disturbance of consciousness and abnormal movements during seizures but may also be attributable at least in part to adverse effects of Antiepileptic drugs (AEDs) which include dizziness and blurring of vision as well as diplopia. About 47% of patients with epilepsy report having at least one injury in the past 12 months yet only 14% had serious injuries **(Asadi-Pooya et al., 2012).**

Causes:

Accidental deaths related to epilepsy are due to trauma, road traffic accidents (RTA's), falls, burns as well as drowning. Standardized mortality ratio (SMR) for accidental deaths among epileptic patients is reported to range between 2.4 and 5.6 **(Hitiris, et al., 2007).**

Domestic, street, and work are, in decreasing order, the most common places for injuries among epileptic patients. Contusions and wounds are the most common injuries followed by abrasions, fractures, brain concussions, sprains, strains, and burns **(Beghi 2009).**

Published risk factors for injuries include the number of AEDs, history of severe seizures, and seizure frequency **(Tellez-Zenteno, et al., 2010).**

Status Epilepticus:

Status epilepticus (SE) is a major medical and neurologic emergency. The incidence of SE was reported to be 41 patients per year per 100,000 population. . The frequency of total SE episodes was 50 per year per 100,000 population. The mortality rate for the population was 22%, 3% for children and 26% for adults **(DeLorenzo et al., 1996).**

Worldwide, it is estimated that there are about one million cases of SE occurring each year with a mortality rate reaching 30% in developing countries **(McCandless, 2012).**

"SE has been broadly defined as seizure activity that continues for 30 minutes, or recurrent seizures without recovery between attacks. The 30-minute duration has been the subject of debate, since it may delay aggressive therapy, particularly when prolonged duration can be predicted in the absence of therapy" **(Aboukhalil et al., 2012).**

Experimental models have shown that neuronal injury occurs after 30 minutes, and refractoriness to anticonvulsants also becomes more prominent after that time **(Rabinstein, 2010).**